Seeing, remembering and thinking about emotions : the effects of lesions ofthe human amygdala on the development of social cognitive skills

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ABSTRACT

There has been a resurgence of interest in the role of the human amygdala in the processing of emotional stimuli, driven largely by human lesion studies. This project develops this work by comparing the effects of the damage to the amygdala acquired in early childhood with the effects of damage in adulthood to a normal amygdala. To further explore the effects of late acquired damage, a group of 21 patients were assessed both before and after surgical excision of the amygdala (performed as part of an anterior temporal lobectomy).

Subjects with early, but not late, acquired lesions of the amygdala showed more extensive deficits in reasoning about the mental states of others, and failed to show the typical pattern of enhanced memory for emotionally arousing material. By contrast, the recognition of facial expressions of emotions was impaired by damage to the amygdala acquired at either stage of development. The results from the cohort of patients tested before and after excision of the amygdala showed that there was little change in performance on the same battery of tests as a result of the operation.

Combining the cross sectional and prospective studies, the results suggest that the amygdala is important in the 'on-line' recognition of facial expressions of emotions. By contrast, an intact amygdala in early development may be required for the acquisition of the ability to reason about the mental and emotional states of others, but not for its execution in adult life. The study illustrates the potential of lesion studies to inform models of the development of social cognition.

Index.

Chapter 1 : Introduction

Chapter 2: Participants in the study.

Chapter 3: The amygdala and emotional memory.

Chapter 8. A prospective study of the effects of an anterior temporal lobectomy on social cognition.

Chapter 9: Developmental models.

Index of Tables and Figures

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6:

Chapter 7

Chapter 8. A prospective study of the effects of an anterior temporal lobectomy on social cognition.

Appended papers (in order)

Shaw, P., B. Brierley, et al. (2005). "A critical period for the impact of amygdala damage on the emotional enhancement of memory?" Neurology **65**(2): 326-8.

Shaw, P., J. Bramham, et al. (2005). "Differential effects of lesions of the amygdala and prefrontal cortex on recognizing facial expressions of complex emotions." Journal of Cognitive Neuroscience **17**(9): 1410-9.

Shaw, P., E. J. Lawrence, et al. (2004). "The impact of early and late damage to the human amygdala on 'theory of mind' reasoning." Brain **127**(Pt 7): 1535-48.

Lawrence, E. J., P. Shaw, et al. (2004). "Measuring empathy: reliability and validity of the Empathy Quotient." Psychological Medicine **34**(5): 911-9.

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Chapter 1: Introduction.

1.1 Introduction

Many theorists have argued that the amygdala is the 'heart' of the social brain. Thus models of the neural underpinnings of aspects of human social behaviour –such as the abilities to detect social signals and form judgments based on these perceptions and to reason about the mental and emotional states of others- have consistently included the amygdala. Papez included the amygdala in his classic neural circuit for the processing of emotionally charged social stimuli (Papez 1937) and early studies in primates suggested that bilateral lesions of the amygdala had profound effects on social and emotional behaviour (Kluver and Bucy 1939). More recent models emphasize the connections between the amygdala and structures such as the orbitofrontal cortex in mediating social cognitive processes (Brothers 1989; Adolphs 2003).

The amygdala lies medially near the pole of the temporal lobes and comprises a group of nuclei which are richly interconnected with both primary sensory and higher order association cortices (Aggleton, Burton et al. 1980; McDonald, Ulfig et al. 2003). Detailed consideration of its anatomy is beyond the scope of this review, and can be found in (Aggleton, Burton et al. 1980)

The objective of this study was to further our knowledge of the role of the amygdala in social cognition, which we take to refer to those cognitive processes subserving human social behaviour. Subjects with lesions of either amygdala were studied in

depth and compared with clinical and healthy control groups. For the subjects with amygdala damage, it was possible to estimate the stage of development during which the damage to the amygdala occurred, which gave an opportunity to explore hypotheses concerning the development of social cognitive skills. In addition subjects who underwent excision of the amygdala as part of surgical treatment for epilepsy were assessed both before and after their operation. Both approaches allow us to address the central question of whether the amygdala damage early in development comprises the development of key skills in social cognition to a greater degree than amygdala damage sustained in adulthood.

1.2 Developmental dimensions

In this initial overview, we examine current attempts to chart the role of the amygdala in the development of social cognitive skills. The dominant approach has been to examine the effects of lesions acquired at different stages of development. The focus of this initial section is thus on neuropsychological studies of the effects of amygdala lesions of the amygdala, particularly the strengths and limitations of existing approaches to the definition of the developmental stage at which damage to the amygdala arises. In the second section, the aspects of social cognition we studied will be considered with a similar focus on the contribution of lesion studies to our understanding of the role of the amygdala in mediating each skill.

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One of the consequences of structural damage to the amygdala is seizures, with the lesion acting as an epileptogenic focus. In subjects with temporal lobe epilepsy (TLE) most have some form of damage to the amygdala, detected through both neuroimaging and electrophysiological studies such as electroencephaolography

(EEG). If the epilepsy is treated surgically through excision of the amygdala and surrounding anterior temporal lobe structures, then a definitive diagnosis of the underlying amygdala pathology can be made. People with TLE have been widely studied, with inferences frequently made on the effects of the associated underlying amygdala damage. In such studies the age of onset of epilepsy has typically been used as an index of the age of onset of amygdala damage. This approach has been most widely used in contrasting the effects of amygdala or hippocampal lesions arising in early childhood with those arising in later life on memory (for example see (Lespinet, Bresson et al. 2002). However some recent studies have used this approach to study the impact of developmental stage of amygdala damage on social cognition, examining the relationship between the age of onset of epilepsy and emotional recognition (Anderson, Spencer et al. 2000; Adolphs, Tranel et al. 2001; Meletti, Benuzzi et al. 2003; Brierley, Medford et al. 2004).

However there are several problems with this approach. Firstly, there is a proportion of patients who have mesial temporal epilepsy with chronic intractable seizures who have no involvement of the amygdala(Zentner, Wolf et al. 1999; Yilmazer-Hanke, Wolf et al. 2000). In these cases obviously the age of onset of seizures in no way reflects the age of onset of damage to the amygdala. It is also sometimes difficult to establish the exact age of onset of seizures. Does this include febrile convulsions which occur in infancy and can then be followed by many years without seizures; does it start at the age of the first seizure; or is the age of onset of the predominant or habitual seizure type? Difficulties are compounded when patients are included who have undergone an anterior temporal lobectomy (ATL) as surgical treatment for their epilepsy. In these patients there are not only the effects of presumed early damage to

the amygdala, but also the damage arising from surgical excision. Deficits may thus reflect the compounded effects of early and late damage to the amygdala.

Damage to the amygdala arising from surgical treatment of epilepsy also varies widely depending on the surgical technique, with considerable variation in the amount of the actual amygdala that is excised (compare the ATL patients described by (Adolphs, Tranel et al. 2005) with those described by (Brierley, Medford et al. 2004). In addition to the amygdala, an ATL also removes structures such as the temporal poles, entorhinal cortex, parahippocampal cortex and anterior hippocampus-structures which may also contribute to social cognition. The other main surgical technique used in TLE is selective excision of the amygdala and hippocampus sparing more anterior structures, although this is a relatively rare procedure. Thus inferences on the specific contribution of the amygdala can only be made with caution from the ATL surgical groups.

Another group of studies has employed subjects with bilateral damage to the amygdala, with the most influential work stemming from patients with Urbach-Wiethe disorder(Adolphs, Tranel et al. 1994; Markowitsch H, Calabrese P et al. 1994; Adolphs, Gosselin et al. 2005). This is a very rare, lipoid storage disease with multiple lipoid infiltrations producing waxiness and thickening of the skin and mucous membranes (Staut and Naidich 1998). In the brain, the disorder manifests as relatively focal bilateral calcification of the amygdala, although involvement of other structures is common (Siebert, Markowitsch et al. 2003).

While studies from such patients have provided vital insights into the amygdala in cognition, there are several limitations in using these subjects to study the development of social cognitive skills. Firstly, the exact age of onset of the disorder is unclear. Although it is generally considered a congenital lesion, there is very little neurioimaging data on Urbach-Wiethe in childhood. One case report of a 5 year old boy with the cutaneous stigmata of the disorder found no evidence of calcification on brain computerized tomography (Galadari and Al-Kuwaiti 2004), and typically neuroanatomical changes are only reported in adolescents and adults (Kleinert, Cervosnavarro et al. 1987; Staut and Naidich 1998). The disorder is degenerative, and thus even if the process starts early in development, its progressive nature will add the sequelae of late damage to early effects.

Most other studies of people with bilateral amygdala damage have subjects whose damage arise from a range of pathologies, such as herpes simplex encephalitis or bilateral surgical excision of the amygdala (the cases are reviewed in chapter 3). In some of the subjects –particularly those with herpes simplex encephalitis such as patient SE described by (Broks, Young et al. 1998)- the age of damage is clearly in adulthood, as the subject had a normal early development. However in others, it is difficult to estimate the exact age of onset of damage to the amygdala. For example, subject DR (described by (Calder, Young et al. 1996) had epilepsy from early childhood which may have compromised the integrity of the amygdala, and later proceeded to surgical excision of the amygdala. Additionally, nearly all of these subjects have extensive involvement of extra-amygdala structures, with obliteration of much of the temporal lobes in herpes simplex cases, which complicates interpretation. In brief, although theoretically very influential, many previous cases of bilateral

amygdala damage present a mix of early and late amygdala damage, limiting the conclusions about the development of social cognitive processes that can be drawn.

1.3.1 Defining the stage of damage to the amygdala- 'early amygdala damage'.

We thus adopt a different approach to defining the stage of amygdala damage, based primarily on pathology. We study a relatively large group of patients who have unilateral lesions incorporating the amygdala, thought on neuroradiological and clinical grounds to be consistent with the presence of a dysembryoblastic neuroepithelial tumour- DNET)(Daumas-Duport, Scheithauer et al. 1988; Raymond, Halpin et al. 1994; Honavar, Janota et al. 1999). DNETs are composed of bundles of axons lined by small oligodendrocyte-like cells and astrocytes. Neurones are relatively sparse and appear to float with random orientation within a mucoid matrix, and have a morphology that can differ from normal cortical neurons. The tumour thus constitutes a major disruption of normal neuronal architecture and function which is reflected in its association with a childhood onset of focal seizures. The neurophysiological abnormalities are often accompanied by metabolic anomalies with the finding of resting hypometabolism in the region of the DNET on fluordeoxyglucode positron emission tomography (FDG- PET). The tumour is also well characterized in terms of its clinical course and pre-operative MRI appearances which allows for a presumptive diagnosis(Kuroiwa, Bergey et al. 1995). There is some debate about the exact age at which these lesions arise, but most authorities argue for a dysembyroblastic origin in the case of DNETs, supported by the presence of multiple and distinct cell lineages in the tumour, the frequent association of cortical dysplasia and evidence of bone remodelling over more superficial lesions(Daumas-Duport 1993; Hirose, Scheithauer et al. 1994). In addition there are several case

reports of familial occurrence of DNET, arising in affected children(Hasselblatt, Kurlemann et al. 2004). By this reasoning the age of onset of damage to the amygdala in patients with a DNET is thus in the embryonic or fetal periods.

The differential diagnosis for a DNET includes other low grade tumours such as gangliogioma and oligodendroglioma (Mc Lendon and Provenzale 2002; Walker and Kaye 2003). The definitive diagnosis of an amygdala tumour is on the basis of pathology, but as most subjects in the early amygdala group in this study had not progressed to excision of the lesion we will later consider the reliability of the making a pre-operative diagnosis of a DNET (chapter 2). A critical point however is that tumours which resemble DNETs neuroradiologically, particularly the major differential of a ganglioglioma, are also thought to arise early in development, presenting with a childhood onset of seizures.

The primary defining feature of all subjects included in our 'early amygdala damage group' is thus a lesion which is consistent with the presence of a DNET. Given the possibility of misclassification in the absence of pathological confirmation of the DNET we use a second, complementary, and more conservative method of establishing the developmental age of an amygdala lesion. This takes the age of onset of habitual seizures arising from the lesions as the age of onset of the lesion itself. This approach has the advantage of reflecting the presence of a DNET that is clinically apparent, acting as an epileptogenic focus with manifest adverse effects on the neurophysiological integrity of local neuronal populations.

In this study both approaches are employed: for the primary analyses the early amygdala group is defined by the presence of a focal amygdala lesion thought to be a DNET (regardless of age of onset of seizures). In further exploratory analyses, the developmental age of the amygdala lesion in the 'early amygdala lesion group' is taken more conservatively to be the age at which it became clinically apparent, acting as an epileptogenic focus.

1.3.2 Defining the stage of damage to the amygdala: 'Late amygdala damage'.

Damage to the amygdala in adult life usually occurs as a result of a temporal lobectomy or amygdalo-hippocampectomy as part of surgical treatment of medically intractable epilepsy. The most common cause of intractable temporal lobe epilepsy (TLE) leading to surgery is mesial temporal sclerosis- a combination of neuronal loss and gliosis (van Paesschen W, Sisodiya S et al. 1995; Kuzniecky, Bilir et al. 1997).

More specifically, hippocampal sclerosis is thought to be the most common cause of intractable TLE, occurring in 50-70% of cases and has been detected in 50% of surgical specimens(Wieser and Epilepsy 2004; Sadler 2006). Amygdala pathology is typically found in the presence of hippocampal sclerosis(Margerison and Corsellis 1966; Hudson, Munoz et al. 1993). However, occasionally a normal amygdala will have been excised, with a large study reporting eleven out of 71 patients with temporal lobe epilepsy to have no involvement of the amygdala, giving a frequency of around 15% (Zentner, Wolf et al. 1999). Another detailed histopathological study reported no major pathology in two out of twenty amygdala from patients who had undergone a unilateral ATL - giving a 10% rate of an unaffected amygdalae in patients with TLE(Yilmazer-Hanke, Wolf et al. 2000). Such subjects thus effectively

acquire damage to a normal amygdala in adult life and can be thus categorized as having 'late' damage to the amygdala.

It is possible to give a precise age of onset of amygdala damage in these subjects: the age of onset of amygdala damage is the age of the operative excision of the amygdala (and surrounding structures). This complements the methods described earlier for giving an estimated age of damage to the amygdala in the DNET group (taken as the age of onset of epilepsy). Thus analyses with age as a continuous variable are possible, in addition to the primary analyses based on the categories of early versus late amygdala damage.

As all these subjects have epilepsy and are on anticonvulsant medications it is clearly important to have an appropriate clinical comparison group(Rapcsak, Galper et al. 2000). We chose a group of subjects with epilepsy arising from similar focal pathologies affecting the temporal or parietal lobe which completely spared the amygdala.

1.4 Studying subjects before and after excision of the amygdala.

In addition to the study of subjects with chronic stable lesions, a group of subjects who underwent operative excision of the amygdala were studied prospectively, with testing both before and after operation. This allows a direct test of the effects of the loss of the amygdala using a prospective within subjects design which removes many of the sources of error that arise when a purely between subjects design is used. This is a novel contribution to the literature as there has been only one case study, and no

group studies, that used this design to examine effects on social cognition of excision of the amygdala(Yamada, Murai et al. 2005).

There are three possible models for the outcome of excision of an amygdala lesion. A 'deficit' model would predict that moving from a pre-operative partial lesion of the amygdala to complete excision would be associated with deterioration in social cognitive functions mediated by the amygdala. This contrasts with a 'recovery of function' model which emphasizes the inhibitory effects that an amygdala lesion may have pre-operatively on interconnected structures. Thus, following complete operative excision of the amygdala, improvement in some social cognitive may occur as interconnected structures (such as the contralateral amygdala) are released from inhibition and can function better. Turning to the final option, if the amygdala has no role in the cognitive process then no deficits would be expected from either a partial or complete lesion, and excision of the amygdala would not be likely to result in a change of function.

1.5 Aspects of social cognition

Several aspects of cognition are examined. Firstly, the process of the emotional enhancement of memory was explored as there is a near consensus that the amygdala plays a pivotal role in such enhancement. Secondly, the effects of damage arising at distinct developmental stages on the ability to recognize the facial expressions of others, using both the so-called basic emotions (fear, happy, sad etc) and more complex expressions (such as being friendly or hostile etc) was examined. Thirdly, the ability to reason about the mental states of others (particularly their emotional

state) was explored. Finally we determined whether amygdala damage at different stages had differing effects on self-reported empathic skills.

1.5.1.Emotional memory

'Emotional memory' is the enhanced, long-term, conscious recall of the facts of emotionally arousing episodes. Such emotionally charged episodes typically resist attrition by time(Brown and Kulik 1977) are recalled in depth and with clarity and confidence(Heuer and Reisberg 1990; Burke, Heuer et al. 1992). Evidence that the amygdala mediates the enhanced long-term recall of emotionally arousing material is compelling and can be found in studies of normal human and clinical populations. Again findings from subjects with amygdala lesions (reviewed in detail in chapter 3) have been critical in developing models of the neural substrate of emotional memory(Cahill, Babinsky et al. 1995).

Using a paradigm which has proved reliable in demonstrating emotional enhancement of memory, we address three central questions. Firstly, do early and late amygdala damage have different effects on the emotional enhancement of memory? There have been no direct studies of this question, and conclusions based on existing lesion studies of patients with bilateral or unilateral damage are open to the criticisms detailed above. Secondly, are the effects of damage to the right or left amygdala the same? Cahill and colleagues initially reported that activity of the right, but not left, amygdala during the viewing of an emotionally arousing film predicted the degree of retention(Cahill, Haier et al. 1996). This group additionally argue that there is an interaction between gender and laterality of amygdala function, with right amygdala activity in men and left amygdala in women predicting later recall of emotional

material(Cahill, McGaugh et al. 2001). Finally, we also tested recent refinements to the role of the amygdala in emotional memory, arguing that it operates as an attentional filter, enhancing memory for the central details of emotionally arousing material at the expense of peripheral details (Adolphs, Denburg et al. 2001; Adolphs, Tranel et al. 2005).

1.5.2 The recognition of facial expressions of emotions.

The ability to recognize facial expressions of emotion is a fundamental social cognitive skill. It has been held to serve communicative functions modulating the likelihood of classes of behaviours (Anderson and Phelps 2000; Blair 2003), or to provide an automatic display of the internal state of the individual(Ekman 1997). Most attention has focused on the recognition and processing of the so-called basic emotions (fear, sadness, disgust, surprise, anger and happiness). These basic emotions are held to be universal communicative signals with distinctive physiology and antecedent events, with a quick onset, brief duration and which evoke automatic appraisal(Ekman 1992). Recently attention has turned to the recognition of more complex emotional expressions. These are harder to define, but several theorists argue that unlike the basic emotions they are dependent for their meaning on social and situational contexts and may vary across cultures. A further subdivision of the complex emotional expressions into social and cognitive expressions has been proposed (Adolphs, Baron-Cohen et al. 2002). Complex social emotional expressions are held to help regulate social interactions and thus include displays of hostility or friendliness etc. These are contrasted with complex cognitive expressions which reflect the inner cognitive state of individuals, for example, whether they are pensive or daydreaming.

The findings from subjects with unilateral or bilateral damage to the amygdala have been particularly influential in the development of theories concerning amygdala function and will be reviewed in detail in chapters 3 and 4. Subjects with bilateral amygdala damage have been repeatedly shown to have deficits in the processing of affective dimensions of faces while sparing the extraction of other forms of information relating to invariant physical attributes(Adolphs, Tranel et al. 1999; Siebert, Markowitsch et al. 2003)- although there are some exceptions(Hamann and Adolphs 1999). The deficits in emotion recognition in subjects with bilateral amygdala damage may extend to more complex expressions. For example one subject with bilateral damage made highly abnormal judgments about how 'trustworthy' another person is on the basis of their facial expressions(Adolphs 2002).

We explore several unresolved issues in this study. Foremost, does early damage to the amygdala have a more deleterious effect on the recognition of emotional expressions than damage acquired late in development? Secondly, we refer to the considerable debate about the exact nature of the affective processing performed by the amygdala. Initial case studies of patients with bilateral damage supported the broad concept that each basic emotion is supported by overlapping but distinct neural substrates(Adolphs, Tranel et al. 1994). Thus a patient SM showed deficits in the processing of emotional expressions of fear only and was intact in the recognition of other basic emotions. This complemented reports of patients who had lesions of the basal ganglia and insula cortex associated with specific impairments in the perception of disgust (Calder, Keane et al. 2000). Since these reports, further case series of patients with bilateral lesions of the amygdala have consistently reported deficits in

the recognition of a wider range of the basic emotions- encompassing perhaps all the basic emotions (Sato, Kubota et al. 2002; Siebert, Markowitsch et al. 2003). In the more complex emotional expressions, Adolphs has argued that it is only social, and not cognitive facial expressions that are affected by damage to the amygdala. (Adolphs, Baron-Cohen et al. 2002) Thus one of the aims of the study is to define the range of basic and more complex emotions that are processed by the amygdala. Finally, we address the possibility of lateralization of processing with unique contributions of the left and right amygdala to the detection of the basic and more complex emotional expressions.

1.5.3. Reasoning about the mental states of others.

The term 'theory of mind' (ToM) has been applied to the capacity to attribute mental states to others in order to understand and predict their behaviour(Premack and Woodruff 1978; Wimmer and Perner 1983). Several models of the neural circuitry mediating this key aspect of social cognition have already been developed on the basis of functional neuroimaging, human lesions and primate studies. The amygdala has been included in some models of ToM reasoning as part of a distributed network which includes other regions of the temporal lobe (particularly the polar cortex and superior temporal gyrus) and frontal lobes (the orbitofrontal cortex and anterior cingulate cortex) (Brothers 1989; Baron-Cohen, Ring et al. 1999; Tager-Flusberg and Sullivan 2000; Abu-Akel 2003; Adolphs 2003; Frith and Frith 2003). Case reports of subjects with bilateral or unilateral lesions of the amygdala suggest that its integrity is necessary for reasoning about the mental states of others(Fine and Blair 2000; Stone, Baron-Cohen et al. 2003)- reviewed in detail later. However, such work is preliminary and unusually the findings of lesion studies conflict with the

neuroimaging data, which does not provide strong evidence for amygdala activation during the performance of theory of mind tasks (Frith and Frith 2003). We thus aimed to examine the possible role of the amygdala in ToM reasoning, focusing again on the possibility of distinct effects of different stages of amygdala damage, and differential effects of left or right amygdala damage.

1.5.4. Empathy.

Finally we consider the impact of amygdala lesions on empathy, using a reliable and valid self report scale of this attribute. Empathy is taken to comprise the ability to understand and predict someone else's mental state and to experience an emotion as the result of someone else's mental state (Baron-Cohen and Wheelwright, 2004). Several lines of evidence implicate the amygdala in empathy - not least its possible role in emotion recognition and theory of mind. We thus ask if lesions of the amygdala have deleterious effects on empathy, particularly lesions which are acquired early in development.

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Chapter 2 : Participants in the study.

2.1 Summary

Details of the inclusion and exclusion criteria for each group are given, and the validity of these criteria critically examined. In addition, power calculations which informed the subject recruitment are shown.

2.2 The 'early amygdala damage' group.

All participants in the clinical groups were recruited from the Regional Neurosciences centre at King's College Hospital, London, a large tertiary referral centre. Most subjects referred to the centre have medically intractable seizures and thus have an assessment for possible surgical treatment of epilepsy in addition to a review of current medical treatment. The assessment includes magnetic resonance imaging (MRI), clinical history and examination, neuropsychometry and electroencephalography (EEG), including scalp and when indicated more invasive monitoring, often with concurrent video monitoring. All patients are discussed at a multidisciplinary meeting of consultant epileptologists, neurologists, neurosurgeons and neurophysiologists where the differential diagnosis of the underlying cause of epilepsy is established. A manual search of all these assessments (approximately 800 were available) was conducted to identify patients whose differential diagnosis included an amygdala DNET. In addition a manual search of all surgical biopsy reports was conducted to identify patients with lesions of the amygdala shown on histology to be a DNET (one patient was identified through this method). Finally, two participants with DNETs were referred directly by consultant neurologists. All

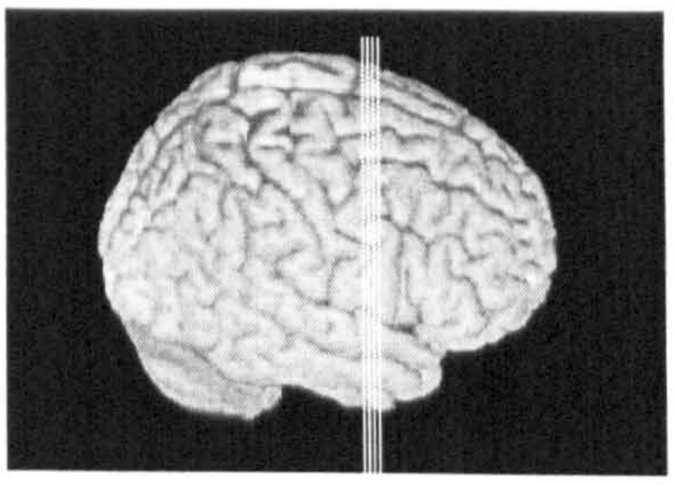
eligible participants were invited by letter and telephone to participate. Five declined. While it is impossible to exclude some selection bias (perhaps those with more severe epilepsy declined for example) the high participation rate and the stated main reason for a decision not to participate (problems with travel to the testing centre) make this unlikely.

The neuroradiological inclusion criteria used in this study to determine the possible presence of a DNET pre-operatively are a modification of the criteria proposed by Daumas-Dupont (Cervera-Pierot, Varlet et al. 1997; Daumas-Duport, Varlet et al. 1999) This group based their neuroradiological criteria on an examination of the preoperative MR appearances of 53 patients with DNETs (later confirmed on histology). They found that the lesion was characterized by a lack of mass effect, no surrounding edema and cortical involvement on both CT and MR imaging.

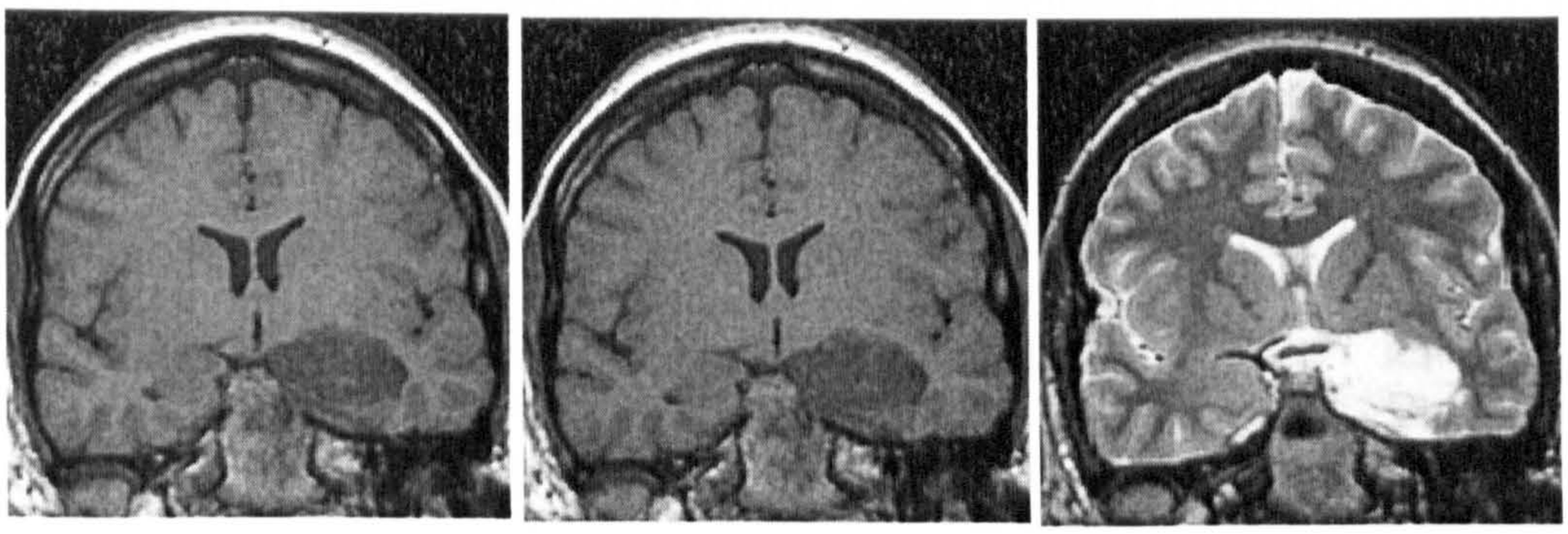
Additional (non-defining) features included decreased signal on T1 weighted magnetic resonance images (present in 95% of subjects), and well demarcated increased signal intensity in on T2 weighted images (present in all cases). Other groups report a similar pattern of a T1 hypodense and T2 hyperdense lesion and propose additional possible criteria such as prominent cystic formations(Raymond, Halpin et al. 1994; Ostertun, Wolf et al. 1996), septations, thick nodular or gyral formation within the tumor (Kuroiwa, Kishikawa et al. 1994; Fernandez, Girard et al. 2003), lack of calcification and bone remodeling over more superifical DNETs (Kuroiwa, Kishikawa et al. 1994; Daumas-Duport, Varlet et al. 1999).

Some typical appearances of DNETs from subjects in this study are given below.

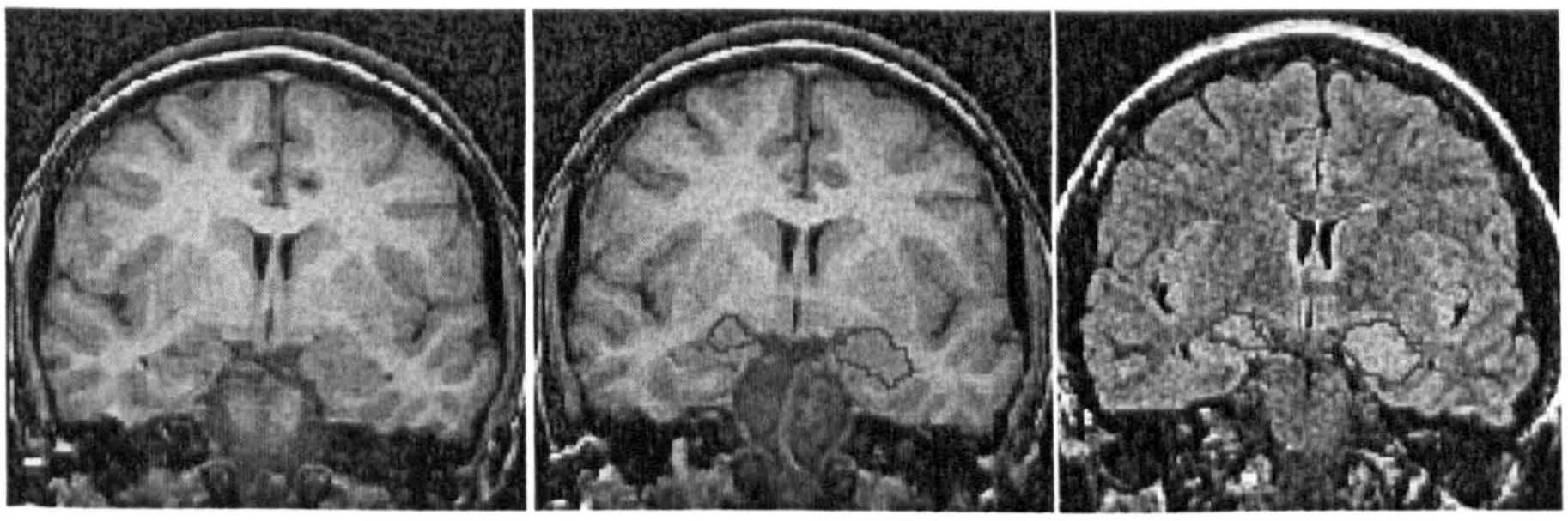
Figure 2.1 Early amygdala damage group



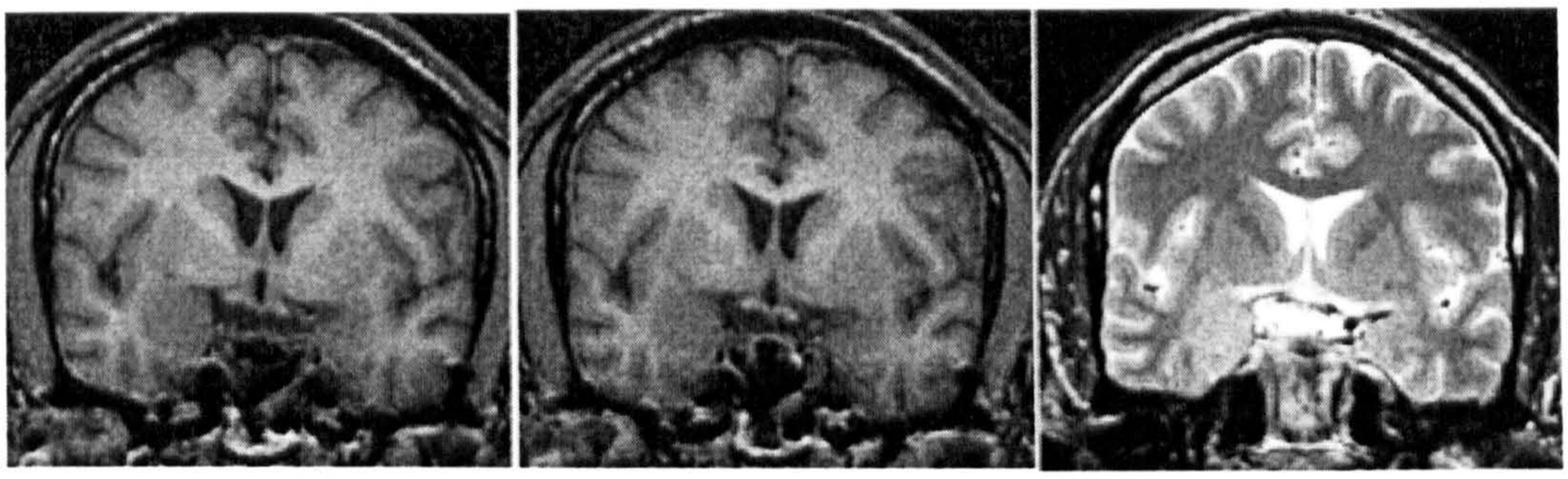
This standard brain illustrates the location of the coronal slices through the amygdala shown below. For most patients T1 weighted MR images are shown on the viewer's left with either a T2 weighted or FLAIR image on the right.



Participant with DNET centred on the amygdala but extending toward the temporal pole and incorporating the anterior hippocampus. The presence of a DNET was confirmed when the patients proceeded to operation. This subject had the largest lesion of any in this group.



Participant with gross enlargement of the left amygdala, seen best on the FLAIR sequences (right).



Participant with gross enlargement of the right amygdala

Although there is thus an extensive literature on the neuroadiolgical appearances associated with a DNET none of these studies constituted a formal exploration of the predictive validity of pre-operative MR appearances. All the studies were retrospective clinico-pathological studies which included only patients with post-operative DNETs and thus could not determine the sensitivity and specificity of the combination of features they propose for diagnosis. However, several of the neuroradiological features listed above aid in differential diagnosis of a DNET from other glioneuronal tumors. For example, oligodendroglioma are typically frontal deep white matter lesions which infiltrate widely and are frequently calcified(Lee and Van Tassel 1989). Low grade astrocytomas often have mass effect and can show contrast enhancement on magnetic resonance imaging. Finally, ganglioglioma- which are the major differential diagnosis- lack the clear margin definition of a DNET, are often calcified, and have mass effect and marked contrast enhancement(Im, Chung et al. 2002; Fernandez, Girard et al. 2003).

The clinical history of a DNET is one of partial seizures with or without secondary generalization with a non-progressive interictal neurological deficit. Daumas-Dupont proposed an age criterion of onset of seizures under 20 which we relaxed to include three subjects with an onset of seizures age 26(Daumas-Duport, Varlet et al. 1999;

Stanescu Cosson, Varlet et al. 2001). One further patient had an onset of seizures aged 24 and had biopsy confirmation of a DNET.

The inclusion criteria for the early amygdala damage group were thus:-

1) A unilateral lesion involving the amygdala

2) The lesion has characteristic neuroradiolgical features of a DNET (non-progressive lesion with no minimal mass effect, no oedema, which is well demarcated on T2 weighted images)

3) A clinical history compatible with the presence of a DNET (of partial seizures with no progressive inter-ictal neurological deficits).

The main differential diagnosis for a DNET is other low grade gliomas, particularly ganglioglioma. It is thought that these lesions may also arise in early childhood and like a DNET they are also highly disruptive of neuronal architecture and thus likely to compromise the development of cognitive functions mediated by the amygdala(Silver, Rawlings et al. 1991; Haddad, Moore et al. 1992; Mickle 1992; Isimbaldi, Sironi et al. 1996; Blumcke and Wiestler 2002). Similarly oligodendrogliomas can be congenital (Narita, Kurotaki et al. 1997). The critical point is perhaps that a DNET is most unlikely to be mistaken for a lesion, such as a high grade glioma- which arises in adulthood.

2.3 Late amygdala damage group.

Most patients in the late amygdala damage group had undergone operative excision of a normal amygdala in adult life (>18 years) as surgical treatment for epilepsy. The normality of the excised amygdala was inferred from post-operative histology which

found no definite pathology of the amygdala. In all cases the amygdala had to be clearly identified in the histology reports. These subjects were identified by a manual search of all histology reports on patients who had undergone an ATL since 1985 at the RNC (approximately 700 reports were examined). Ten potential participants declined. Again selection bias is possible, but the high rate of participation suggests that those who participated were likely to be representative of this population.

In addition to the ATL subjects acquiring, one patient acquired damage to the amygdala as a result of radiotherapeutic treatment in adult life of a vascular anomaly in the temporal pole. One patient had a more aggressive tumour centred on the left temporal pole which was thought to have expanded rapidly to include the amygdala in adult life. The tumour excision incorporated most mesial temporal lobe structures including the amygdala.

Figure 2.2 A participant with late acquired damage to the amygdala

Participant with a typical right anterior temporal lobectomy, with en bloc resection of all structures stretching 4.5cm from the temporal pole with complete excision of the amygdala. Pre-operative MRI showed no abnormality in the amygdala and there was no abnormality on histology of the resected tissues.

Where possible preoperative MRIs were also obtained on these patients and a normal volume of the amygdala established using the guidelines below. In some cases pre-operative MR were not performed (in pre-1990 cohort) or could not be obtained from other neuroimaging centres.

In collaboration with Dr B Brierley precise guidelines were developed for a protocol to measure the amygdala which had high intra and inter-rater reliability and validity(Brierley, Shaw et al. 2002). This was based partly on a systematic review and meta-analysis of previous neuroimaging studies which was used to gain accurate measures of the volume of the amygdala and hippocampus.

Pre-operative structural MR images acquired on a 1.5 Tesla GE N/Vi Signa System (General Electric, Milwaukee, WI, USA) at the Maudsley Hospital, London were available on nine of the subjects in the late amygdala group. Images were acquired with a 3-D inversion recovery prepared fast spoiled GRASS T1-weighted data set. These T1-weighted images were obtained in the coronal plane with 1.5mm contiguous sections. TR was 9.1ms, TI was 450 ms, TE was 2.0 ms and the flip angle was 20 degrees with one data average, a 240mm field of view and a 256x256x124 pixel matrix. This data set provided complete coverage of temporal lobes and almost complete coverage of frontal, occipital and parietal lobes with resolution 0.86x0.86x1.5mm. The acquisition parameters for all data sets were chosen with the aid of a software tool for optimising image contrast (Simmons A, Arridge SR et al. 1996). Images were transferred to a SUN workstation and displayed using the DISPIM software package (Plummer DL, 1992). The images were zoomed to a magnification of 2.5. The amygdalae were outlined manually by two raters (BB and

PS) using a mouse-driven cursor, according to the method described below. The volume for each structure was obtained by outlining the region of interest. DISPIM automatically calculated the area of the region marked for each slice, and then these values were summed for each structure; the total number is then multiplied by slice thickness (1.5mm). The intracranial volume was also calculated for each subject. This was done by measuring the area every tenth slice, and multiplying the sum of the values by 15 (10 x 1.5).

In the volumetric work, the amygdala is defined excluding the subiculum, and including the ambient gyrus, uncus and all nuclei. The volume of the amygdala is measured in a posterior-anterior direction on 1.5mm coronal slices using structural MRI scans depicted on DISPIM. The hippocampus, measured first, is posterior to and partially overlapping with the amygdala, and its border, once defined, serves as a critical guide for the amygdala boundaries. Anatomical landmarks external to the amygdala, are used in each successive coronal slice, to generate reliable and repeatable volumes. The anatomical landmarks are in brief:

The posterior border is marked by the appearance of the mamillary bodies

The superior border can be traced without using external landmarks if a small layer of white matter is clearly visible, thus excluding the globus pallidus and putamen Otherwise, the superior border of the amygdala is defined by drawing a straight line laterally from the endorhinal sulcus to the fundus of the inferior portion of the circular sulcus of the insula.

The medial boundary of the amygdala in anterior slices can be defined by drawing a line from the inferior side of the uncal notch to the semianular sulcus.

The inferior border of the amygdala is the superior border of the hippocampus in first 3-5 posterior slices of the amygdala (Convit A, et al., 1999). However, when unclear, the inferior border of the posterior amygdala is marked arbitrarily by a horizontal line drawn medially from the head of the temporal stem to the medial border of the amygdala: the amygdala is taken to be grey matter superior to that line.

The lateral border of the amygdala is formed by the inferior horn of the lateral ventricle or by white matter extending medially to the uncal notch. In anterior slices the white matter tract may be difficult to identify, therefore the lateral border is defined by a vertical line drawn between two landmarks, as can be seen in figure 3-6. The first is the most inferior and lateral point of the white matter bordering the amygdala and the second point lies on the superior border directly above the first point. The perpendicular line joining these two points will define the lateral border. In posterior slices the white matter tract forming the lateral border is the temporal stem.

The anterior border is arbitrarily and consistently measured when the lateral sulcus closes to form the endorhinal sulcus.

Total intra cranial volume is calculated for control subjects and patients, and used to calculate the correction factor employed to control for group differences in head size. The intra cranial volume is taken to be all structures within the inner table of the skull to the level of the foramen magnum, using the dura as its marker where visible. The pituitary and cavernous sinuses were excluded.

Patients' amygdala volumes were measured using the above protocol, and all volumes expressed as a proportion of total intracranial volume. This is probably not the

optimal method for adjustment for differences in intra-cranial volume, but is suitable given the small numbers of subjects which makes regression based correction difficult (proposed by (Jack CR. Jr. 1994). All the subjects in the late amygdala damage groups had amygdala volumes (expressed as a proportion of ICV) which fell within one standard deviation of the mean volume (again expressed as a proportion of ICV) of the normative sample of 32 healthy controls [mean proportion right amygdala/ICV=0.001642, sd 0.000256; left amygdala mean=0.001647, sd=0.000229]

Table 2.1 Pre-operative amygdala volumes in participants in the late amygdala damage group

Subject code	Right amygdala (mm^3)	Left amygdala (mm^3)	Intracranial volume (mm^3)	Adjusted right amygdala	Adjusted left amygdala
Late2	2356.90	2749.50	167803.0	.0140456	.0163853
Late8	1833.00	2108.00	139989.0	.0130939	.0150583
Late9	2633.80	2408.90	169358.3	.0155516	.0142237
Late6	2232.10	2191.80	139967.9	.0159472	.0156593
Late1	2488.20	2440.10	152215.4	.0163466	.0160306
Late3	2104.70	1960.40	128731.2	.0163496	.0152286
Late5	2217.80	2258.10	135479.8	.0163700	.0166674
Late7	2340.00	2193.10	137498.4	.0170184	.0159500
Late4	2684.50	2581.80	156073.3	.0172002	.0165422

In further pilot work we have shown that this volumetric method is sensitive to the presence of even minimal sclerosis associated with minimal neuronal loss(Lambert, Brierley et al. 2003).

The subjects were tested at a mean of 4.3 years after the ATL (standard deviation of 4.3 years) with a range of 6 months to 13 years.

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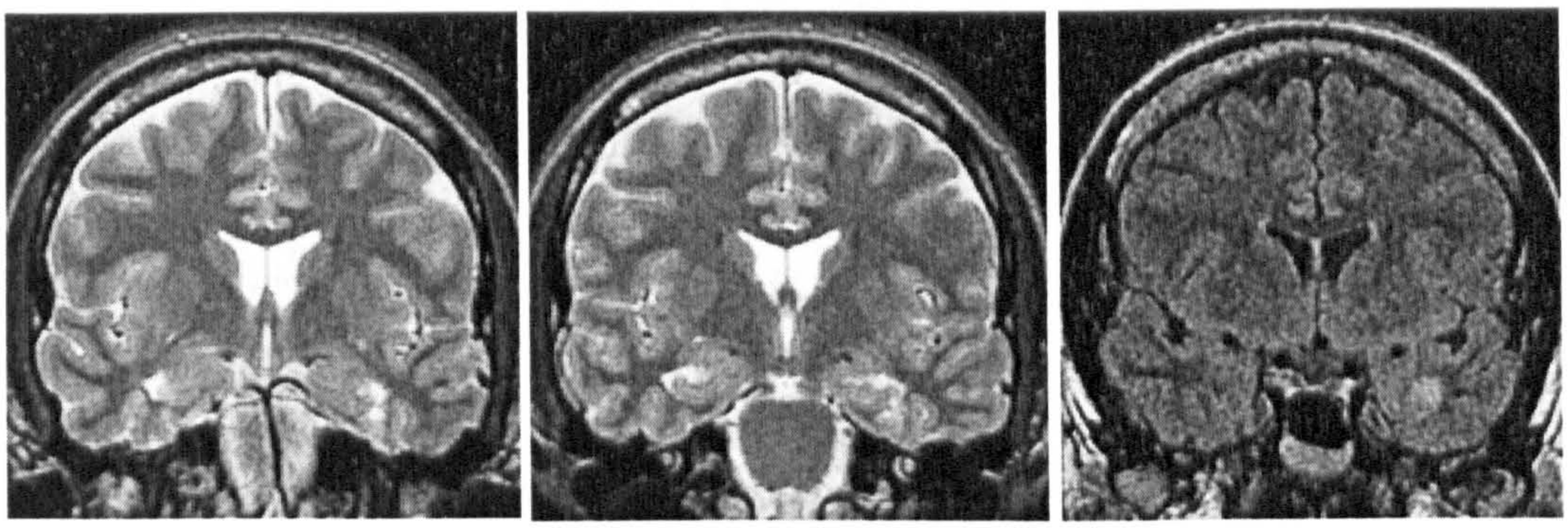
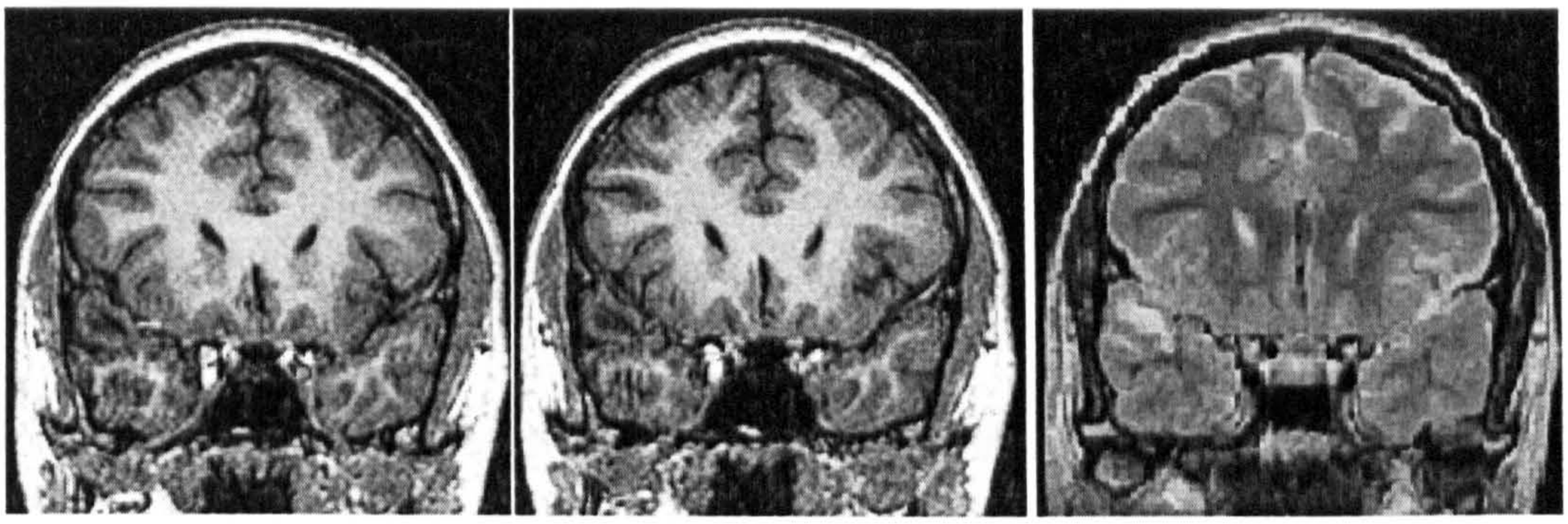
2.4 Clinical control group

Subjects in the clinical control group were recruited from the same epilepsy surgery programme. All subjects in this group had structural lesions, apparent on MRI, which were held to be acting as an ictal focus. In all cases the lesions completely spared the amygdala in the opinion of consultant neuroradiologists. Twelve were within the temporal lobe, two in the parietal lobe, one in the insula and one in the occipital lobe. The lesions were thought to be DNETs in six participants, of which four were confirmed on histology, although one subject recently showed tumour progression and further excision resulted in a re-classification of the tumour. The remaining pathologies were of a cavernoma or arteriovenous malformation (N=2); an epidermoid cyst (N=1); developmental anomalies of uncertain nature (N=3); cortical dysplasia (N=1); a ganglioglioma (N=3); and a surgical excision of the insula for uncertain pathology (N=1).

Figure 2.3 Clinical controls



Participant with a lesion in the parahippocampus extending to head of hippocampus seen best on FLAIR sequence (on right, with T2 weighted on left). Histology confirmed a DNET and normal amygdala.



Participant with a lesion in the right temporal opeculum seen as a hypodense region on the T1 weighted images (left) and hyperdense on T2 sequences (right).

2.5. Healthy controls

Healthy control subjects were recruited in part from a database of volunteers with no history of psychiatric or neurological disorders. Some healthy volunteers were recruited through personal contacts.

There was no payment for participation. The study was approved by the Ethics Committee of the Institute of Psychiatry and all subjects gave written informed consent.

2.6 Exclusion criteria.

The general exclusion criteria were of age under 18, IQ less than 80 or English not being the first language and other progressive neurological disorders affecting the central nervous system.

A history of mental illness was not an exclusion criterion in the amygdala damage and clinical control groups and was determined from the medical records (all patients in the epilepsy surgery programme have a psychiatric history taken as part of the examination). A full mental state examination was not conducted at the time of testing. However all patients in the epilepsy surgery programme are referred to a consultant neuropsychiatrist attached to the unit if a mental disorder is suspected by neurologists or nurse specialists.

Four patients (two in the early amygdala group, one in the late amygdala and one in the clinical control group) were being treated for depression. One patient in the late amygdala group had a history of social anxiety and depression and was being treated with cognitive behavioural therapy alone. One patient in the late amygdala damage group had a psychotic disorder and was taking a low dose of trifluoperazine (a typical antipsychotic); another patient in this group started to take low dose antipsychotic risperidone (an atypical antipsychotic) after the time of assessment as she began to express persecutory delusions. One patient in the clinical control group and one in the late amygdala group had a history of bipolar affective disorder, but were euthymic at time of assessment. One was taking sodium valproate both as a mood stabiliser and anticonvulsant; the other patient was taking carbamazepine as an anticonvulsant and lithium as a mood stabiliser. As schizophrenia and bipolar affective disorder have been linked with some deficits in social cognition, analyses were conducted both with and without these subjects and the main results will be presented in the relevant passages. Overall the results did not change with the exclusion of these subjects.

2.7 Participant accrual

At the end of the study there were 16 participants in the early amygdala, 17 in the late amygdala damage groups and 17 clinical controls. Not all subjects completed each task. The number of healthy control participants also varied between tasks, in part reflecting power issues (discussed below).

2.8 Clinical variables

2.8.1. Medication

All subjects in the early amygdala and clinical control groups had epilepsy and were taking anticonvulsants. Details of the medication at time of testing in these groups are given in Table 2.2. Two subjects in the late amygdala damage group had stopped anticonvulsants as they had been seizure free for several years. Five other patients in the late amygdala damage group were seizure free post-operatively for a shorter period of time (less than 2 years) and as anticonvulsants are withdrawn cautiously in this operative group, all remained on medication in slowly reducing amounts. The proportion of patients in each clinical group who were on monotherapy did not differ significantly (χ^2=0.30, p=0.86).

Table 2.2 Anticonvulsant medication at time of testing.

	Early amygdala (N=16)	Late amygdala (N=17)	Clinical controls (N=16)
Monotherapy	9	7	8
No medication	0	2	0
Medication at time of testing			
Carbamazepine	9	10	10
Phenytoin	3	1	1
Valproate	0	2	4
Phenobarbitone	1	0	0
Long acting	2	2	2

benzodiazepines			
Newer agents			
Gabapentin	0	1	3
Topirimate	3	0	2
Lamotrigine	2	2	1
Levetricetam	2	1	0
Vigabatrin	0	0	1

2.8.2. Seizure burden

There was no significant difference between the groups in the overall frequency of all seizures (see table 2.3 below). The late amygdala group had fewer seizures as might be expected as they had undergone surgical treatment for epilepsy. This abolished seizure activity in seven of the subject completely, reduced seizure frequency in three patients and had no beneficial effect in six patients.

Table 2.3 Clinical characteristics of participants.

	Early damage	Late amygdala damage	Clinical controls	Tests of significance
Age of onset (years)	13 (9)	16 (10)	16 (8)	F(2,46)=0.84, p=0.44
Age at testing (years)	33 (10)	36 (11)	29 (7)	F=2.1, p=0.13
Frequency of seizures	9.4 (6.9)	3.9 (7.3)	8.3 (7.9)	F=2.52, p=0.09
Status epilepticus (ever)	1	0	1	-

The age of onset of epilepsy was taken as the start of habitual seizures. Three patients had a history of infantile febrile convulsions (two in the early amygdala damage and

one in the late amygdala damage group). These were not considered to be the age of onset of seizures as the febrile convulsions were isolated. .

2.8.3 Aura

The amygdala may be important for the subjective experiences of fear. In this regard it is interesting to note that degree of amygdala pathology has been correlated with the presence of sensation of fear immediately prior to the onset of seizure activity (an epileptic aura)(Cendes, Andermann et al. 1994; Van Paesschen, King et al. 2001). In our subjects fear and closely aligned emotional states of extreme anxiety and panic were found in seven of the early amygdala patients as part of an aura. However fear auras were not exclusive to this group and were found in two of the subjects in the late amygdala damage group (who had a normal amygdala pre-operatively) and in six of the clinical controls- none of whom had amygdala damage. The proportion of patients in each group with these aura did not differ (χ^2=4.4, p=0.11). Similarly, dysmnestic experiences such as deja and jamais vu are often linked with the amygdala as an epileptogenic focus, and may reflect its role in the formation of emotionally charged memories. However, again we did not find any clear evidence for a link with amygdala damage, with dysmnestic aura reported by similar proportions of subjects in each clinical group (three in the early amygdala damage, one in the late amygdala damage and two in the clinical control group). A history of status epilepticus, which can result in severe sclerotic change in the mesial temporal lobe was present in only one subject in the early amygdala and one in the clinical control group.

2.9 Power calculations

The power calculations were based mainly on the results of existing findings available in the literature at the time of study design. In addition results from the PhD thesis of Dr B Brierley into the neuropsychological correlates of anterior temporal lobectomy were also used with her consent (Brierley 2002). Some of these findings have been published (Brierley, Medford et al. 2004). In some cases the research question was entirely exploratory, particularly the work on the effects of anterior temporal lobectomy on social cognition. Power calculations were made using nQuery and PASS/NCSS software.

2.9.1 Emotional memory

There is a large literature on the emotional enhancement of memory using a paradigm originally designed by Heuer and Reisberg, and adapted by Cahill and others(Cahill and McGaugh 1995). This comprises of a series of photographs and accompanying text, in which an emotional, central section of the story follows and precedes neutral sections. Memory for the story is tested one week after presentation with a multiple choice questionnaire. An index of emotional enhancement of memory is calculated as a proportion of correct recognition scores for the emotional passage minus neutral passage over combined neutral and emotional passage recognition [(emotional – neutral)/ (emotional + neutral)], a positive score thus indicating superior memory for emotional material. For the power calculation, we assumed that the early amygdala damage group would behave similarly to subjects with bilateral amygdala damage (details of each individual index derivation given in chapter 3). The indices for these subjects range from -4 to -26 (indicating a complete loss of emotional memory), and we conservatively took the upper value of the range as our subjects have unilateral rather than bilateral damage and thus might show an attenuated loss of emotional

memory. (At the time of the power calculation a study by Papps and colleagues which reported intact emotional enhancement of memory and an index of +18 in a patient with bilateral amygdala damage was not available (Papps, Calder et al. 2003)). The late amygdala damage group were assumed to behave similarly to the 30 patients who had an anterior temporal lobectomy in the study by Brierley and colleagues, (with a mean index of emotional enhancement of 7.2 and standard deviation of 16).(Brierley, Medford et al. 2004) The clinical control group was assumed to have the same degree of emotional enhancement as 17 subjects with generalized epilepsy from the same study (mean index 8.4, SD 11). Finally values for the healthy control group were also taken from this study (mean 7.6, sd 10). To have 80% power to detect group differences of these magnitudes (assuming a common SD of 11) with an alpha of 0.05, it was estimated that a total of 65 participants was needed, 13 in each clinical group and 26 healthy controls.

2.9.2 The detection of complex emotional expressions.

The task used to assess the ability to detect complex emotional expressions was the revised version of the 'Reading the Mind in the Eyes Task'(Baron-Cohen, Wheelwright et al. 2001). The estimated performance for the healthy control group was taken from the original report of the task (mean 27, sd 4). Pilot data by the author on five clinical controls suggested a mild deficit with a median score of 25 (range 22-28). We assumed that the late amygdala and clinical control groups would have a similar mean of 25 and a common sd of 4. In the absence of any lesion studies using this task we assumed that the early amygdala group would show a level of impairment similar to adults with Asperger's syndrome (scoring a mean of 22 with sd 4) (Baron-Cohen, Wheelwright et al. 2001). It was calculated that 60 subjects, 12 in each

clinical group and 24 healthy controls would be needed to detect the estimated effect (with 80% power and an alpha of 0.05).

2.9.3 Theory of mind reasoning

Calculations were based on the performance of adult subjects on Happe's Strange Stories(Jolliffe and Baron-Cohen 1999). We assumed that healthy and clinical control subjects would score in line with the healthy adults in the Joliffe et al study and that subjects with early amygdala damage would score similarly to people with Asperger's syndrome. The outcome measure was the total scores for correct mental state justifications (healthy control 99% SD1.3; Asperger's syndrome group –mean 85%, SD 10.8%: a common SD of 10% was assumed for the power calculation). It was also assumed that participants with late amygdala damage would show no impairment. To detect group differences of the expected magnitude, a total of 50 subjects (ten in each clinical group and 20 in the healthy control group) would be needed (power 80% with alpha 0.05).

Finally for the faux pas task we assumed that deficits in the early amygdala would be of a similar magnitude to those reported for patients with orbitofrontal lesions who show impairment on the task (and scored a mean of 80% with a SD of approximately 10% in the measure of correct detection of a faux pas)(Stone, Baron-Cohen et al. 1998). The late amygdala, clinical control and healthy groups were all taken as behaving as the clinical controls in the Stone et al study, who had dorsolateral prefrontal cortex damage (and scored 100%, and are assumed to have a similar SD of 10% for the purposes of the power calculation). It was estimated that 4 in each clinical group and eight in the healthy

control group would be needed to detect group differences of this magnitude (power 80% and alpha 0.05).

Combining the various power estimates we thus aimed throughout the study to include at least 14 patients in each clinical group and 28 healthy controls. In most of the experiments, the numbers estimated from the power calculations were met, suggesting that the study had sufficient power to reject or accept null hypotheses if the assumptions underlying the power calculations are accepted.

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Chapter 3: The amygdala and emotional memory

3.1 Summary

There is compelling evidence that the amygdala plays a role in enhancing memory for emotionally arousing material. We explored the effects of amygdala damage arising at different stages of development on this emotional enhancement of memory. Comparisons were made with clinical controls with focal lesions sparing the amygdala and healthy controls subjects. We found that early damage to the amygdala was associated with a complete loss of emotional enhancement of memory, with a significant correlation between the estimated age of amygdala damage and degree of loss of this emotional enhancement. Indeed there was a suggestion of a complete reversal of the typical pattern with early amygdala damage subjects recognizing neutral information better than emotionally charged material. The study provides further evidence for the central role of the amygdala in emotional memory, and demonstrates different effects on emotional enhancement of memory dependent on the stage of development at which damage arises.

Some of the findings of this chapter have been published in the journal *Neurology* (paper is appended at end of thesis).

3.2 Developmental effects of amygdala damage on emotional enhancement of memory.

The role of the amygdala in human memory has shifted to the fore of cognitive science, fueled by a convergence of findings from functional neuroimaging, animal models and human lesion studies. There is evidence that the amygdala plays a role in the encoding of affectively charged material, the consolidation and retrieval of emotional memories and more controversially may act as a site for the long term storage of emotional memories.

The role of the amygdala in encoding emotional memories is supported by repeated demonstrations that the degree of its activation correlates with the later recall of emotionally charged, but not affectively neutral, material in functional imaging studies in humans(Cahill, Haier et al. 1996). Loss of the amygdala in animals and humans also impairs the acquisition of implicit emotional memories, as assessed by conditioned fear (LaBar, LeDoux et al. 1995; LeDoux 2000).

Two lines of evidence suggest that the amygdala may influence encoding through augmenting attention to emotionally salient stimuli and thus boosting initial depth of stimulus processing. Firstly, loss of the amygdala abolishes the attentional blink phenomenon (the benefit for the perception of aversive material in conditions of limited attention)(Anderson and Phelps 2001), highlighting the importance of the amygdala in directing attention. Secondly, in functional imaging studies activation in the visual cortex during passive viewing of fearful faces correlates highly with amygdala activation which has been attributed to rapid feedback from the amygdala to sensory areas through a subcortical pathway (Morris, Friston et al. 1998). Such

feedback from the amygdala on the initial detection of an emotionally salient stimulus may lead to greater attention during later perceptual processing.

Following encoding, the amygdala may also be pivotal in the consolidation of emotional memories, primarily through interaction with other brain regions, in processes which may be modulated by neurohormonal responses to emotional arousal. In animals, after learning of a conditioned fear response, pharmacological manipulations (such as infusions of catecholamine agonists into the basolateral amygdala) enhance memory, an effect which is not prevented by induction of a temporary amygdala lesion prior to a retention test (Packard, Cahill et al. 1994). The enhanced memory is however blocked by similar temporary lesions of the hippocampus or caudate nucleus induced shortly before a retention test. In humans, two studies induced an arousal response immediately after a stimulus was encountered using either a pharmacological or pain intervention and found that such post-stimulus arousal enhanced later memory(Cahill and Alkire 2003; Cahill, Gorski et al. 2003). This effect was only found for stimuli which were rated as emotionally arousing prior to the study, suggesting that the amygdala's modulation of memory consolidation may be most marked for affectively salient stimuli. Similarly blockade of beta adrenergic receptors impairs enhanced emotional memory implying that the consolidation effect relies on the neurohormonal response to arousal and stress (Cahill, Prins et al. 1994). Pharmacological blockade and augmentation of central noradrenergic transmission respectively decrease and increase the degree of retrograde amnesia for negatively valenced and retrograde hypermnesia for positively valenced stimuli (Hurlemann, Hawellek et al. 2005). Functional imaging studies have demonstrated that the amygdala modulates activity in anterior temporal and prefrontal

lobe structures during the encoding of emotionally arousing but not neutral material (Kilpatrick and Cahill 2003; Dolcos, LaBar et al. 2004; Richardson, Strange et al. 2004). This interaction may also be modulated by the adrenergic system as adrenergic blockade at the time of encoding both abolishes enhanced amygdala activation at encoding and activation of the hippocampus at retrieval(Strange, Hurlemann et al. 2003). Such correlational studies provide indirect evidence that strong memory for emotionally arousing material may reflect adrenergic modulatory influences from the amygdala on other memory storage processes occurring distally.

The amygdala is also active during the retrieval of emotional memories. Such activation is marked when subjects accurately recall seeing an emotive stimulus, with clear recollection of the details of the episode when the stimulus was presented ('remembering' it has been seen before), rather than merely having a feeling of familiarity with the stimulus ('knowing' it has been seen before)(Sharot, Delgado et al. 2004). The role of the amygdala in underlying the enhanced feeling of memory for emotional events has been confirmed at an interval of a year(Dolcos, LaBar et al. 2005).

Recent work has moved from laboratory based paradigms of declarative memory in humans to examine the effects of amygdala damage on the recollection of autobiographical memories. Buchanan and colleagues found that subjects with right ATL recalled fewer unpleasant memories than subject with a left ATL and healthy controls (Buchanan, Tranel et al. 2006). This suggests either a positive bias in retrieval due to right amygdala damage, or perhaps an impaired recognition of unpleasant experiences as negative events.

A more contentious issue is whether the amygdala is itself the site of storage of affective memories. In favour of a storage model, there are animal studies suggesting that the basolateral nucleus of the amygdala is necessary for both the acquisition and retention of Pavlovian fear conditioning in animals (LeDoux 2000; Gale, Anagnostaras et al. 2004). Against this view human functional imaging studies find that the amygdala is active during the acquisition of conditioned fear but is no longer active after the conditioned fear response is acquired (Buchel, Morris et al. 1998; LaBar, Gatenby et al. 1998).

There is substantial corroboration of the amygdala's pivotal role in modulating emotional enhancement of memory from human lesion studies. One of the most widely used paradigms is the Heuer and Reisberg test(Heuer and Reisberg 1990; Cahill and McGaugh 1995). This comprises of a series of photographs and accompanying text, depicting a story of a boy who suffers a terrible car accident, after which he is rushed to theatre in hospital. This emotional, central section of the story follows and precedes neutral sections that set the scene and describe the repercussions, respectively. Memory for the story is tested one week after presentation with a multiple choice questionnaire. Retrieval of information relevant to emotional and neutral pictures is compared, and the data used to calculate an emotional index score as above. To allow comparison of results from previous studies using this test, we derived an emotional enhancement index from the original data. This is calculated as a proportion of correct recognition scores for the emotional passage minus neutral passage over combined neutral and emotional passage recognition [(emotional – neutral)/ (emotional + neutral)]. This index thus assesses the degree to which

emotionally arousing material is better recognized than neutral material and adjusts for overall level of performance. Table 3.1 below illustrates the results from studies of subjects with bilateral and unilateral amygdala damage which have used this paradigm. It has generally been shown that bilateral lesions of the amygdala are associated with a loss of enhanced recall of the emotionally disturbing passage. There is one exception - patient DR- who though described as a bilateral lesion patient, is notable for the relative sparing of much of the right amygdala and the basolateral region of the left amygdala(Papps, Calder et al. 2003). By contrast, unilateral damage patients show largely preserved emotional enhancement of memory(Brierley, Medford et al. 2004).

Table 3.1: review of studies of emotional memory using Heuer and Reisburg's test of emotional memory. The index of emotional enhancement has been estimated using data available from the original papers.

	Subjects	Side	Pathology	Emotional index (e-n)/(e+n)
Current study	Healthy controls	-	-	7.9 (s.d.10)
(Cahill, Babinsky et al. 1995; Adolphs, Cahill et al. 1997)	SM	Bilateral	Urbach-Wiethe- damage in early development	-6.19
	BP	Bilateral	Urbach-Wiethe	-5.11
(Phelps, LaBar et al. 1998)	SP	Bilateral	Excision of R ATL in adult life. L amygdala reactive gliosis	-5.73
(Brierley, Medford et al. 2004)	JC	Bilateral	R amygdala sclerosis. L congenital tumour and subsequent ATL	-4.30
	CB	Bilateral	L amygdala sclerosis. R ATL in adult life	-14.9
	CH	Bilateral	Bilateral sclerosis and hydrocephalus. Patient had neonatal brain damage and subsequent adult excision of R ATL	-26.4
(Papps, Calder et al. 2003)	DR	Bilateral	Bilateral surgical lesions in adulthood of the amygdala extending rostrally.	18.2
(Adolphs, Cahill et al. 1997)	Anterior TL (N=2)	R	Surgery in adulthood	17.5
	Anterior TL (N=6)	L	Surgery	6
(Brierley, Medford et al. 2004)	Anterior TL (N=14)	R	Surgery	12.8
	Anterior TL (N=11)	L	Surgery	7.4

Laterality effects have been considered in several lesion studies. Using the Heuer and Reisburg paradigm, a loss of the emotional enhancement for verbal, but not visual, material was reported in left anterior temporal lobectomy subjects(Tomaz and Frank 2003).

In other paradigms of declarative emotional memory, the results of loss of an amygdala are less apparent (see Table 3.2 below).

Table 3.2 Declarative emotional memory in patients with unilateral or bilateral damage assessed by other paradigms.

		STUDY 1		STUDY 2		STUDY 3
Pathology		Group study: Resection of anteromedial temporal lobe (incl. A) for intractable TL 10 R and 12 L sided		Group study: Resection of R anteromedial temp. lobe (incl. A, for intractable TL, 13 L and 13 R		Case study : Resection of R anteromedial temp. lobe (incl. A, for intractable TL, + L-side lesion (gliosis & signal hyper-density on T-2 images)
Extent of amygdala damage		Removal of 70-80% of amygdala on operated side		100% removal of R A on operated side		
Damage external to amygdala		3.5cm resection of ant., middle & inf. temporal gyri., dissection of occipito-temporal fasciculus. Removal of H, para-H		3.5cm resection of ant. middle & inf. temporal gyri., dissection of occipito-temporal fasciculus. Removal of H, para-H		
Patient profile: **(M:F)** **(mean age - years)** **(education – years)**		R: sided 3:7 31.1 ±8.1 ? ed.	L sided: 5:7 38.8 ± 7.9 ? ed.	R sided: 7:6 36 ±10 13 ±2 ed.	L sided: 3:10 38 ±9 14.2 ±2 ed.	F 54 years old 12 ed. R- handed
Neuropsychology		Subset from 13 pt's with FIQ= 99 ±14	Subset from 13 pt's with FIQ=107±12	FIQ = 99 ±14	FIQ = 107 ±12	WAIS-R – VIQ=104, PIQ=107, FIQ=106
Early vs. late onset of illness / duration of illness		From group of 13 with seizure onset @ 9 ±10yrs	From group of 13 with seizure onset @ 7 ± 7 yr's	Age of seizure onset: 9 ±10	Age of seizure onset: 7 ± 7	Epilepsy diagnosed @ 3-4 yr's old; right temporal lobectomy
PARADIGM: **9 +ve, 9 –ve, 9 neutral words; equally arousing** **Free recall @ 1 min.**	NORMAL RESULT Signif superior recall for +ve & -ve words			Trend towards sup. recall for +ve & -ve words (12/13 pt's)	Superior recall for +ve & -ve words (11/13 pt's)	Superior recall of emotional words vs. neutral
Neut. words used by sbj. to create +ve, -ve & neut sentences. Free recall @ 5 min's	Sup. recall for neutral words in –ve & +ve sentences			Sup. recall for neutral words in –ve & +ve sentences (11/13 pt's)	Sup. recall for neutral words in –ve & +ve sentences (12/13 pt's)	Superior recall for neutral words in –ve & +ve sentences
Free recall of 20 neutral, 20 emotional taboo words, immediately & at 1 hour	Superior recall of taboo words, with incr in taboo recall advantage *over time*	Superior recall of taboo words, but equal rates of forgetting emotional & neutral words *over time*	Sup. recall of taboo words, but equal rates of forgetting emot. & neutral words *over time* (marked deterioration for emot. words)			Superior recall of taboo words but with NO increase with time for taboo word recall

KEY: TL – temporal lobe epilepsy MCQ – multiple choice questionnaire
A – amygdala H - hippocampus
L – left R – right

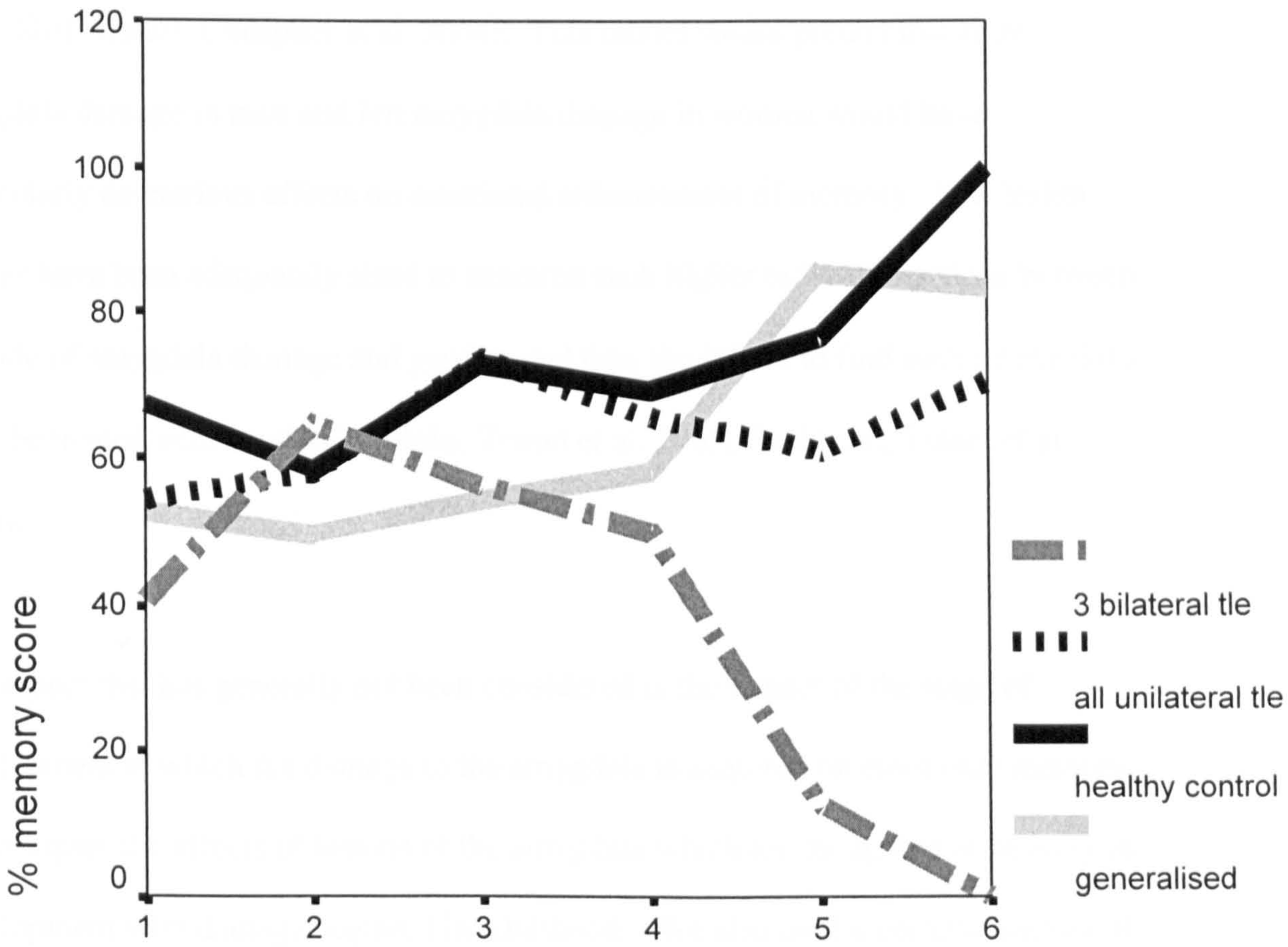
References: (STUDY 1) (LaBar KS & Phelps EA, 1998); (STUDY 2) (Phelps E, LaBar K, & Spencer, 1997); (STUDY 3) (Phelps E, et al., 1998).

Subjects with either unilateral or bilateral amygdala damage showed normal enhanced recall of emotional words and neutral words embedded in an emotive rather than neutral context (Phelps, LaBar et al. 1997; Phelps, LaBar et al. 1998). However, these stimuli, although valenced, did not cause physiological arousal. When intensely arousing socially taboo words were used, subjects with amygdala damage failed to show the normal increase in recall with time. The authors suggested that the amygdala is necessary for the correct encoding and consolidation of arousing, but not emotional, words *per se*.

Brierley found evidence to support this contention in a study of 28 subjects with amygdala damage (Brierley, Medford et al. 2004). She used a similar paradigm to Phelps and colleagues, with two sets of 42 sentences. Within each set, half the sentences were emotional and arousing, half were neutral. The inclusion of an emotional or neutral *target* word determined the tone of the sentence. Memory for the target words was tested at one hour, and the difference between forced choice recognition for the emotional and neutral words was compared. Similarly, memory was compared for neutral words '*embedded*' in either emotional or neutral sentences: these were the emotional and neutral embedded words. The typical enhanced recall for emotional words was intact in subjects with unilateral and in two of three subjects with bilateral amygdala damage. However, in further analyses the stimuli were categorized according to the degree of arousal associated with the word (using the Affective Norms for English Words (ANEW) (Bradley MM & Lang PJ, 1999). There was a loss of enhanced recall for the ten most arousing words in subjects who had a right ATL and those with bilateral amygdala damage, (with relative preservation of

emotional enhancement of recall for left ATL subjects). Indeed the subjects with bilateral amygdala damage showed a complete reversal of the normative pattern of enhanced recall for arousing words. This is illustrated below in Figure 3.1 which demonstrates the typical improved recognition of words which are more arousing in healthy controls, and contrasts this with the reverse pattern in the three subjects with bilateral amygdala damage.

Figure 3.1 The relationship between the degree of arousal of individual words and later recognition memory.



Key: tle=anterior temporal lobectomy subjects; generalized= clinical controls with generalized epilepsy

Two of the three bilateral amygdala damage subjects additionally showed a tendency to recall neutral words embedded in unarousing sentences better than neutral words embedded in arousing sentences- the complete opposite of the normative pattern (see (Brierley 2002) chapter 5 and (Brierley, Medford et al. 2004).

Laterality effects are also frequently reported in functional imaging studies (for a review see (Zald 2003). It has been further suggested that laterality may depend on gender, with right amygdala activation noted during encoding in men and left amygdala in women during the encoding of emotional arousing material(Cahill, Haier et al. 2001; Cahill, Uncapher et al. 2004). This model would predict that right amygdala damage in men and left amygdala damage in women would have particularly deleterious effects on emotional enhancement of memory. Few lesion studies have been adequately sized to examine such higher order interactions between the side of amygdala damage and gender, and thus the failure to find such interactions must be treated with caution(Adolphs, Tranel et al. 2005; Buchanan, Tranel et al. 2006).

One aspect that has generally not been considered is the impact of the stage of development at which the damage to the amygdala is acquired on emotional memory. We compare the effects of lesions of the amygdala which are thought to arise early in development with damage acquired in adulthood. We also used a complementary, if more conservative method of establishing the developmental age of an amygdala lesion, as the age of onset of habitual seizures caused by the lesion.

3.3 Hypotheses.

We predicted that early unilateral lesions of the amygdala would be associated with more deleterious effects on emotional memory enhancement than lesions acquired in adulthood. We explored the possibility of both laterality and gender effects. Specifically we tested the hypothesis that right amygdala damage in men and left amygdala damage in women would be associated with marked loss of emotional enhancement of memory, thus testing for a significant interaction between the side of amygdala damage and gender.

3.4 Methods

3.4.1 Participants – see Table 3.3.

All clinical subjects were recruited from the surgical epilepsy programme at the Regional Neurosciences Centre at King's College Hospital, London.

1) Fourteen subjects with focal amygdala lesions, four with right and ten with left sided damage. All subjects in this group had focal lesions of the amygdala with minimal, if any, extension beyond this structure. The neuroradiological and clinical histories of these subjects were given earlier. As these pathologies are thought to arise in early development, this group is designated the 'early amygdala damage' group.

2) Sixteen patients who had undergone en bloc surgical resection of the anterior temporal lobe to treat medically intractable epilepsy. As all patients in this group had a pre-operatively normal amygdala completely excised in adulthood they are designated the 'late amygdala damage group'. The normality of the preoperative

amygdala was inferred from normal histology reports and in most cases a normal volume of the pre-operative amygdala as detailed in the previous chapter.

3) Twelve subjects with focal non-amygdala lesions - 'clinical controls'. All subjects in this group had focal lesions which completely spared the amygdala. The lesions were made up of non-progressive tumours (ten subjects) vascular malformations (three subjects) and one subject each with a developmental anomaly and epidermoid cyst.

4) 47 healthy controls were recruited in part from a database of subjects willing to act as volunteers in research with no psychiatric or neurological disorders.

3.4.2 Tasks

Clinical groups completed the vocabulary, digit span, comprehension and similarities subscales for verbal IQ, and the block design and object assembly subscales for performance IQ from the Weschler Adult Intelligence Scale- third revision UK version. An estimate of IQ was obtained from the National Adult Reading (Nelson 1982) test for the neurologically intact control subjects. Memory was assessed with the immediate and delayed logical memory test from the Wechsler Memory Scale- third revision (1997)

The modified Heuer and Reisburg test of emotional memory was used(Cahill, Babinsky et al. 1995). This comprises 11 picture slides and accompanying text, depicting a story of a boy who suffers a terrible car accident, after which he is rushed to theatre in hospital. This emotional, central section of the story follows and precedes

neutral sections that set the scene and describe the repercussions, respectively.

Memory for the story is tested one week after presentation with a multiple choice questionnaire.

3.4.3 Analysis

Retrieval of information relevant to emotional and neutral pictures is compared, and the data used to calculate an emotional index score as above. An emotional enhancement index was calculated as a proportion of correct recognition scores for the emotional passage minus neutral passage over combined neutral and emotional passage recognition

Index of emotional enhancement= 100 x [(emotional – neutral)/ (emotional + neutral)].

The correlation between the estimated age of damage to the amygdala and index of emotional enhancement was calculated. The age of damage to the amygdala in the focal early amygdala lesion group is taken conservatively as the age of onset of habitual seizures. The age of damage to the amygdala in the 'late' operative group with a normal amygdala pre-operatively is taken to be the age of the operative excision of the amygdala and surrounding structures (for justification see earlier chapters).

3.5 Results

3.5.1 Demographic and neuropsychological details of participants are given in Table 3.3.

Table 3.3: demographic and neuropsychological characteristics.

	Early amygdala damage group	Late amygdala damage	Clinical controls	Healthy controls	Tests of significance
Side of damage right; left	4 : 10	12 : 4	4 : 8	-	χ^2=81.6, p<0.001
Gender: male;female	6 : 8	9 : 7	5 : 7	19 : 28	χ^2=1.2, p=0.74
Age at testing- (mean and s.d.)	32 (10)	37 (10)	29 (8)	35 (12)	F=1.7 p=0.15
Verbal IQ (mean and s.d.)	98 (15)	98 (15)	89 (14)	108 (10)	F=8.1, p<0.001
Logical memory – immediate	6.1 (2.8)	7.8 (3.2)	8.6 (4.1)	-	F=1.9, p=0.16
Logical memory – delayed	6.2 (2.6)	7.8 (3.6)	9.4 (4.0)	-	F=2.8, p=0.08

*clinical controls< healthy controls p=0.01.

3.5.2 Heuer and Reisburg task.

Recognition scores (% correct) for each section of the task are given in Table 3.4. A repeated measures ANOVA showed a main effect for group (F[3,85]=13.1, p<0.001, with all clinical groups impaired relative to healthy controls, Bonferroni adjusted p<0.05). There was also a main effect for type of material (F([1,85]=9.8, p=0.002, with emotional material recognized better than neutral, p=0.002). The significant

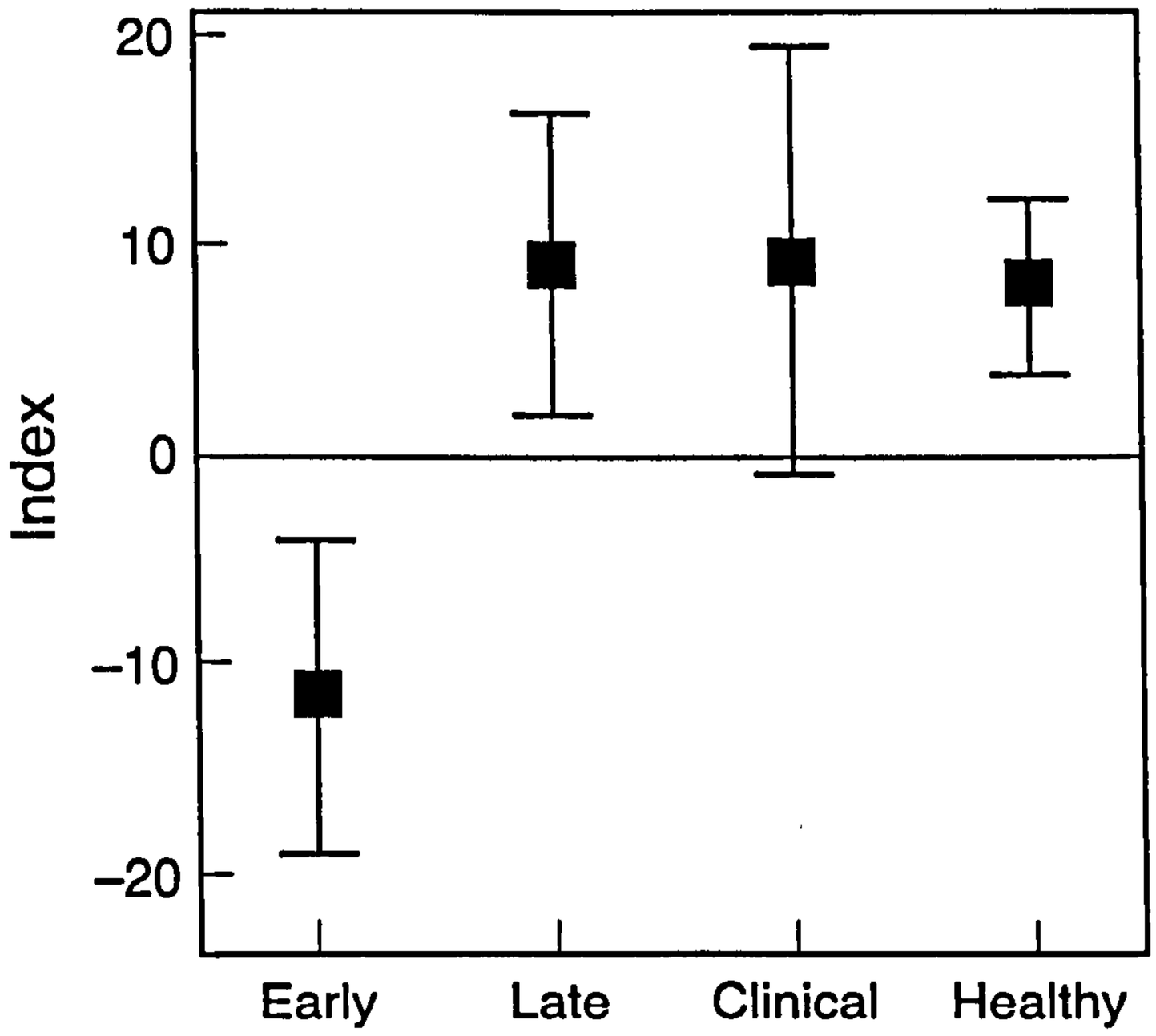
Table 3.4 Scores in recognition in the Heuer and Reisburg task

	Early amygdala damage group	Late amygdala damage	Clinical controls	Healthy controls
Heuer and Reisberg task: Neutral – mean % (s.d.)	40.5 (7.2)	37.3 (12.0)	38.5 (8.8)	49.2 (12.5)
Emotional- mean % (s.d.)	32.6 (8.7)	45.3 (15.3)	46.7 (11.4)	58.5 (13.3)

interaction between group and type of material ($F(3,85)=8.2$, $p<0.001$) was explored using the index of emotional enhancement. In a one-way ANOVA, there was a group difference in this index ($F[3,68]=9.2$, $p<0.001$)- see Figure 3.2. The early amygdala damage group showed less emotional enhancement of memory than all other groups (all $p<0.001$, Bonferroni corrected). All other pairwise group differences in the index of emotional enhancement were not significant.

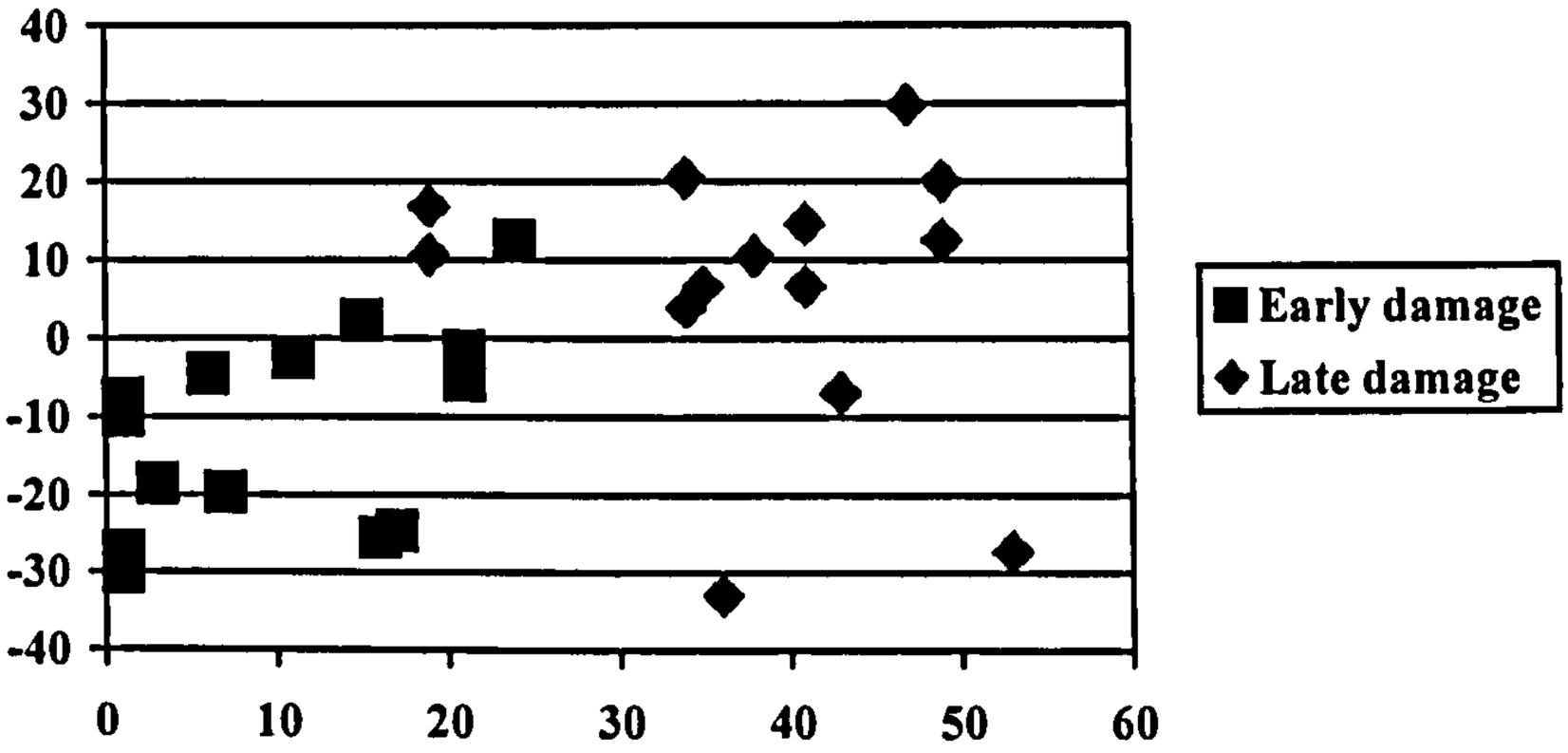
All but the early amygdala damage group showed the typical pattern of superior recognition of emotionally arousing over neutral material. In paired t tests for emotional vs neutral material: for healthy controls $t(46)=5.2$, $p<0.001$; for the late amygdala group $t(15)=3.4$, $p=0.004$; for clinical controls showed similar superior recall of emotionally enhanced material, but this did not quite reach significance $t(11)=1.98$, $p=0.07$. This pattern was not seen in the early amygdala group who in fact demonstrated poorer recognition of emotionally charged relative to neutral material ($t(13)=3.3$, $p=0.005$).

Figure 3.2: mean index of emotional enhancement (with 95% CI) for the early and late amygdala damage groups, and clinical and healthy comparison groups.



We calculated the correlation between the estimated age of damage to the amygdala and the index emotional enhancement- see Figure 3.3. Spearmans' rank correlations between the age of amygdala damage and index of emotional enhancement were highly significant (rho 0.5, p=0.007). Thus earlier damage to the amygdala is associated with a greater degree of loss of emotional enhancement of memory.

Figure 3.3 Correlation between the estimate age of damage to the amygdala (x axis) and the index of emotional enhancement (y axis).



3.5.3 Laterality and gender.

The side of damage (right or left) and group (early, late, clinical controls) were entered as fixed factors with the index as the dependent variable in a 2 way ANOVA. The results (mean index and SD) are given in Table 3.5. There was the expected main effect of group ($F(2,36)=7.8$, $p=0.002$) but no main effect of side of damage ($F(1,36)=0.21$, $p=0.65$), and no significant interaction between side and group ($F(2,36)=0.88$, $p=0.42$.

Table 3.5: index of emotional enhancement of memory for each clinical group separated by side of damage.

Side	Group	Mean	Std. Deviation	N
Right	Early amygdale	-14.8	9.4	4
	Late amygdale	12.0	14.5	12
	Clinical controls	9.5	20.0	4
Left	Early amygdale	-10.3	14.1	10
	Late amygdale	1.1	9.0	4
	Clinical controls	9.0	15.2	8

Possible effects of gender were examined (including all four groups- the early and late amygdala and clinical and healthy controls). There was the expected main effect for group ($F(3,81)=9.2$, $p<0.001$) but no main effect for gender ($F(1,81)=0.26$, $p=0.61$) and no significant interaction ($F(3,81)=1.2$, $p=0.31$)- see Table 3.6 below. When analyses were restricted to those with amygdala damage (early or late) there was likewise a main effect of group ($F(1,26)=16.5$, $p<0.001$) but no main effect of gender ($F(1,26)=1.6$, $p=0.22$) and no significant interaction ($F(1,26)=0.45$, $p=0.51$).

Table 3.6 Index of emotional enhancement for each group by gender.

Group	Gender	Mean	Std. Deviation	N
Early amygdala	Male	-9.9	10.2	6
	Female	-12.9	15.1	8
Late amygdala	Male	13.5	7.7	9
	Female	3.9	18.7	7
Clinical controls	Male	3.7	10.2	5
	Female	13.2	19.0	7
Healthy controls	Male	10.9	11.6	19
	Female	7.3	12.8	28
All participants	Male	7.4	12.8	39
	Female	4.4	16.6	50

We then tested for an interaction between gender and side in emotional memory, by entering these as fixed factors in a 2-way ANOVA. As this hypothesis only concerns the amygdala, analyses were restricted firstly to all subjects with amygdala damage (late and early). The results for each side by gender are below. There was no main effect of side of damage ($F(1,26)=3.0$, $p=0.09$), gender ($F(1,26)=0.98$, $p=0.33$) and no interaction ($F(1,26)=0.20$, $p=0.66$).

Table 3.7 Index of emotional enhancement in the amygdala damage groups only, divided by side of damage and gender.

Side	Gender	Mean	Std. Deviation	N
Right	Male	8.7	13.6	10
	Female	-.2	23.7	6
Left	Male	-4.9	13.2	5
	Female	-8.2	14.5	9

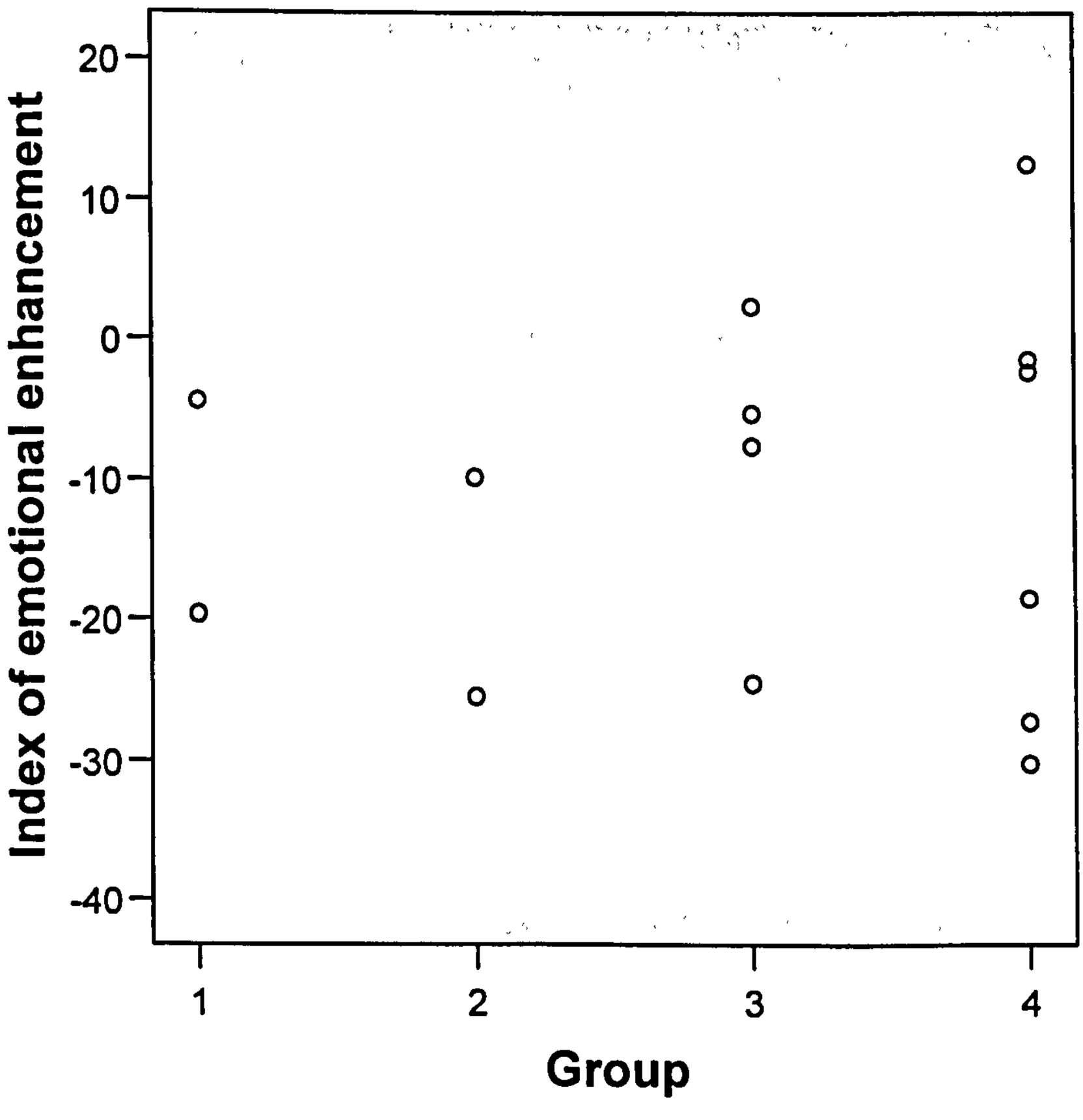
Similar analyses were problematic in the early (focal) amygdala damage group only given the small number of subjects in each cell. However a scatterplot of each individual in the early amygdala group, divided into four groups by gender and side is shown below (right male, right female, left male, left female) in Figure 3.4 . There was no overall group difference in the index of emotional enhancement $\chi^2=0.95$, $p=0.81$.

3.4.4 Possible moderating variables.

There was no significant correlation with the age of onset of habitual seizures and index of emotional enhancement for the clinical groups(Pearson's rho=0.23, p=0.14)

suggesting that an early age of onset of seizures per se, regardless of the location of the epileptogenic focus, did not account for the findings. The pattern of results was not accounted for by group differences in age, verbal IQ, standard measures of declarative memory, or seizure frequency none of which correlated significantly with the index of emotional enhancement (all $p>0.05$), nor removed the effect of group when entered as covariates in ANCOVA.

Figure 3.4 Scatterplot of index of emotional enhancement for early amygdala damage group divided by side and gender.



Key 1=right males; 2=right females; 3=left males; 4=left females.

3.5 Discussion

3.5.1 Summary of main findings

As predicted, damage to the amygdala, when occurring early in development, was associated with a loss of emotional enhancement of declarative memory. By contrast, subjects who underwent excision of the amygdala as part of an anterior temporal lobectomy in adult life showed preserved emotional enhancement of memory. There was no evidence to support the hypothesis that right sided damage in men and left sided damage in women was particularly detrimental to emotional enhancement of memory.

The loss of emotional enhancement of memory in the early amygdala damage subjects is comparable with that reported among most, but not all, patients with bilateral amygdala damage, many of whom also acquired amygdala damage to at least one of the amygdalae early in development. This developmental dimension may also explain the previous reports of largely preserved emotional enhancement of memory among patients with unilateral amygdala damage (Brierley, Medford et al. 2004).

Emotional enhancement of memory was not just lost in those with early amygdala damage but completely reversed. This highlights the degree of disruption to the amygdala dependent circuitry for modulating memory of material which is perceived as emotionally arousing.

We can only speculate on the neuroanatomic bases of why early, rather than late, amygdala damage disrupts emotional memory. Perhaps early amygdala damage may disrupt the formation of tracts linking the amygdala to other structures involved in the formation of emotional memories. This may explain why the presence of a largely intact contralateral amygdala was not sufficient to preserve emotional enhancement of memory in the subjects with early damage. Indeed the neuranatomical sequelae of early damage may be more profound than the effects of the circumscribed severing of tracts that occurs following surgery.

Thus early amygdala damage might result in impaired encoding, in part through a failure of the amygdala to feedback rapidly through a possible subcortical route to primary sensory cortices. This possibility is supported by the association between degree of damage (indexed by T2 relaxation times) in patients with amygdala sclerosis and activation of the visual and fusiform cortices during the viewing of fearful but not neutral faces (Vuilleumier, Richardson et al. 2004). No details were given in this study on the estimated age of damage to the amygdala, and thus it is not possible to assess whether those with presumed earlier amygdala compromise show the most anomalous patterns of connectivity as we would predict. As noted earlier, amygdala damage may also result in a failure to orient to salient stimuli(Anderson and Phelps 2001), although if this was the only mechanism underlying reduced emotional enhancement, then impairment might also be expected in those with surgical excision of the amygdala in adulthood.

Failure in consolidation of memory traces may play a role. Early amygdala damage could conceivably lead to more severe disruption of the reciprocal connections between structures such as the anterior hippocampus and amygdala. Such anatomical reciprocity may mediate the co-dependence of amygdala and hippocampal activation during emotional-memory encoding, demonstrated by Richardson and colleagues(Richardson, Strange et al. 2004). Using subjects with varying degrees of hippocampal and amygdala sclerosis, they found that encoding-related hippocampal activity for successfully remembered emotional items correlated with the degree of left amygdala sclerosis, whereas amygdala-evoked activity to subsequently remembered emotional items correlated with the degree of left hippocampal pathology. Again it would be intriguing to repeat this experiment in subjects in whom accurate estimates of age of amygdala damage can be made. Early amygdala damage may also disrupt post-encoding consolidation through subtle perturbations of neurohormonal response to emotional arousal, perhaps due to a failure of formation of connections to the hypothalamus, although there are no specific data to address this possibility.

Early amygdala damage may also impair the retrieval of emotional memories, although the amygdala seems specifically involved in the degree of confidence of accuracy of recall (Sharot, Delgado et al. 2004; Dolcos, LaBar et al. 2005), an aspect we did not assess in our paradigm. Finally, the different results between the early and late amygdala damage groups cannot be explained by the concept of the amygdala as a site of storage for long-term emotional memories: this would predict equal impairment in both groups.

Another possibility is that compensation for damage to the amygdala occurring in adulthood may more complete- perhaps reflecting the recruitment of developed redundant brain systems, or use of other cognitive strategies to give emotional enhancement in memory. If such cognitive compensation existed, then we might expect there to be a correlation between the degree of emotional enhancement of memory and time since the anterior temporal lobectomy. However, there was no such significant correlation (Spearman's rho=0.22, p=0.40), although the small numbers of subjects means this result cannot be regarded as definitive.

In terms of the cognitive underpinnings, it could be argued that the early amygdala damage patients did not perceive the stimuli as emotionally arousing: the entire sequence is perceived as affectively neutral and thus encoded as 'neutral' material. Hence the fault does not lie in enhancement of memory, but rather in anomalous perception. We did not exclude this possibility as neither behavioural nor neurophysiological measures of arousal at time of encoding were made. However, previous studies on subjects with bilateral amygdala damage, which was often complete and arising early in development, showed normative ratings of emotionality of the same stimuli(Adolphs, Cahill et al. 1997), if not neurophysiological evidence of arousal. Additionally if the stimuli were all perceived as affectively neutral, then later retrieval should be the same for all portions of the passage. However there was evidence than the early amygdala damage group showed a reversal of the normative pattern of retrieval, recognizing 'emotional' portions worse than neutral ones.

Early amygdala damage may result in a failure of the development of early implicit emotional memory, typically assessed using fear conditioning paradigms. Although abnormal fear conditioning has been noted in patients with anterior temporal lobectomies, it is possible that some of these subjects had damage in early development, and also that subjects with definite early lesions would be more impaired (LaBar, LeDoux et al. 1995). Perhaps failures of the more rudimentary forms of emotional memory formation weaken the foundations for the development of more complex declarative emotional memories.

3.5.2 Limitations.

It was also noted that one study using this test found an interaction between the modality of material and side of amygdala damage, with a loss of emotional enhancement for verbal but not visual material among subjects with left ATL. (Tomaz and Frank 2003). However, closer examination of the Heuer and Resiburg test shows that many of the stimuli are not easily categorized as either verbal or visual and rely on both modalities either at encoding or retrieval. Thus we chose not to explore the effects of modality using this test. This makes it difficult to exclude the possibility that the early amygdala damage patients may have found the task challenging due to its verbal nature. The task can also be criticized as the nine different pictures differed considerably in visual complexity. Additionally the task cannot address the issue of whether it is the emotionally aversive nature of the material or its arousing nature that accounts for enhanced recall. The two dimensions of valence and arousal are highly correlated, although other paradigms have successfully disentangled the factors and suggest that arousal, rather than emotional colouring, may the critical quality in emotional memory (Dolcos, LaBar et al. 2004). Finally the task involves forced

choice recognition, and we cannot thus the possibility of a different pattern of results if a free recall paradigm had been used.

We did not find any evidence of laterality effects, although one major limitation of the study was the imbalance between the early and late amygdala damage groups with respect to side of damage. It is noteworthy however that there are other aspects of amygdala function which also do not appear to demonstrate lateralisation: these include fear conditioning, associative learning using facial expressions and the perception of complex mental states(LaBar, LeDoux et al. 1995; LaBar, Gatenby et al. 1998; Burton, Gilliam et al. 1999; Boucsein, Weniger et al. 2001; Adolphs, Baron-Cohen et al. 2002; Delgado, Frank et al. 2005).

The significant correlation between the age of damage to the amygdala and extent of loss of emotional enhancement of memory must be interpreted with caution. Firstly, within each group (early and late amygdala damage) there was no significant correlation, suggesting that the overall correlation is driven by the between group effect. This emphasizes the limitations in using this approach to define a precise sensitive period for the development of normal emotional enhancement of memory.

There were also some differences in medication between the groups, with two patients in the late damage group on no medication, compared to the early amygdala damage group all of whom were on anticonvulsants. Several factors argue against medication having a major effect. Firstly all subjects in the clinical control group were medicated and still showed emotional enhancement of memory. Additionally, a recent study

from our group included a group of patients with severe generalized epilepsy, all of whom were on anticonvulsants and still demonstrating intact emotional enhancement of memory.(Brierley, Medford et al. 2004).

A recent refinement in the theory of amygdala function developed on the basis of lesion studies holds that the amygdala mediates enhancement for emotionally arousing gist only, and that damage may actually result in a decreased recall for emotionally arousing peripheral detail (Adolphs, Denburg et al. 2001; Denburg, Buchanan et al. 2003; Adolphs, Tranel et al. 2005). In this view the amygdala acts as an attentional filter that is activated when emotionally charged information, particularly aversive material, is being encoded. In the first study of this question, patient SM, who has bilateral amygdala damage stemming from Urbach-Wiethe disease, showed poorer memory for the gist of aversive stimuli relatively worse than healthy controls or subjects with unilateral temporal lobectomy. Conversely she also remembered visual detail for the same aversive stimuli better - a complete reversal of the typical pattern(Adolphs, Denburg et al. 2001). In an extension of this work, the amount of loss of memory for gist in an emotionally arousing condition, but not overall recall, was shown to correlate with the degree of amygdala damage. Additionally gist memory was intact in patients with lesions of the medial temporal lobes which spared the amygdala(Adolphs, Tranel et al. 2005). This is in keeping with the concept of the amygdala focusing attentional resources on central, salient information.

Cahill and colleagues have used the Heuer and Resiberg test to examine this hypothesis(Cahill and van Stegeren 2003). They categorized portions of the passage

as pertaining to central information or gist, and peripheral information. Gist or central information was determined in these studies through consensus of several raters as being any information which cannot be removed or altered without changing the fundamental story line. Peripheral information or detail was defined as pertaining to information which was largely incidental and could be easily removed or altered without changing the story line. In an exploratory analysis of our data we looked at data classifiying it according to the level of detail (whether central or peripheral information) and level of emotion (neutral as opposed to emotionally arousing material). In all groups there were main effects for the level of detail (gist recognized better than peripheral detail) and level of emotion (emotionally arousing recognized better than neutral) but no interaction between these factors [details available from candidate]. Thus even in the healthy control group there was no evidence that for emotionally arousing material central or gist material was better recognized than peripheral material. This suggests that the Heuer and Reisburg paradigm may not be ideal for an assessment of the hypothesis that there are amygdala dependent mechanisms for the allocation of attentional resources.

Cahill and colleagues have made a further refinement to the model of the amygdala as directing attention to emotionally arousing gist, arguing for gender effects(Cahill 2003). They reason that as men encode emotional material with the right amygdala and the right hemisphere in general may be relatively biased towards the processing of more global, holistic aspects of a stimulus or scene, then disruption of processes of consolidation of emotional memory in men (through blockade of beta adrenergic receptors) would abolish gist memory in men(Delis, Robertson et al. 1986; Lane RD, Fink GR et al. 1997; Ivry and Robertson 1998). Conversely in women, the left

amygdala is activated during encoding of emotional stimuli, and the left hemisphere, it is argued, is relatively biased towards more local, finer detail processing of the stimuli, then similar interventions would disrupt recall of peripheral detail in emotionally arousing stimuli. We did not have sufficient numbers in this study to test for such higher order interactions (the test is of a four way interaction between gender, side of amygdala damage, and level of detail and level of emotion).

3.7 Conclusion.

We demonstrate that unilateral lesions of the human amygdala arising early in development, but not in adulthood, are associated with a loss of the expected superior retrieval of emotionally arousing over neutral material.

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Chapter 4: The recognition of facial expressions of the basic emotions

4.1 Summary

Data from people with focal brain lesions implicate the amygdala in the perception of facial expressions of the basic emotions. It is unclear whether the age at which damage to the amygdala is sustained plays a role in determining the extent of later impairments in processing facial expressions of emotions. Previous studies suggest that there may be an association between an earlier age of amygdala damage and impaired recognition of facial expressions of emotions. However, studies have typically used either adults with bilateral amygdala damage (which prohibits a consideration of possible lateralisation of amygdala function), or patients who had an unilateral anterior temporal lobectomy, (which complicates an assessment of the specific contribution of the amygdala). To address these issues, we compared subjects with relatively focal unilateral lesions of the amygdala, acquired early in development with subjects who had a normal amygdala excised in adulthood. Subjects with focal lesions which spared the amygdala acted as a clinical control group in addition to healthy volunteers. In a test of the rating of the intensity of emotional expressions subjects, the early and late amygdala damage groups both showed abnormal ratings for all emotional categories combined, attributable mainly to abnormal ratings for facial expressions of fear and sadness. This suggests that damage to amygdala acquired at any stage of development may have adverse effects on the processing of facial expressions of emotion, in line with a role for the amygdala in 'on-line' processing of emotional stimuli. Damage to the right amygdala was associated with more impaired labeling of facial expressions of fear and more anomalous ratings of emotional facial expressions than damage to the left amygdala. Whereas left amygdala damage, and clinical and healthy controls rated fear as looking

similar to surprise, the right amygdala damage subjects rated fear as being similar to sadness.

4.2 Introduction.

Evidence from lesion studies has implicated the amygdala as a pivotal component of the circuitry mediating the perception of emotional expressions in others. We have already mentioned some of the unresolved issues in the field. Firstly, in line with the principal theme of this thesis it is unclear whether the stage at which damage is acquired to the amygdala determines the degree of later deficits in emotional recognition. Initial work into this issue has relied heavily on inferences drawn from the effects of bilateral damage of the amygdala in subjects with Urbach-Wiethe (UW) disorder which is associated with relatively focal calcification of the amygdala(Siebert, Markowitsch et al. 2003). Patients with this disorder have been found to have impairment in the emotion recognition- see table 4.1 for a review(Adolphs, Tranel et al. 1994; Siebert, Markowitsch et al. 2003). As mentioned earlier it is difficult to estimate the exact age of onset of amygdala damage in UW, although it is generally assumed to be a degenerative disorder with progressive calcification, which may start in childhood. By contrast, patients who acquired bilateral damage to the amygdala in adulthood due to herpes simplex encephalitis showed no such emotion recognition impairments(Hamann, Stefanacci et al. 1996; Hamann and Adolphs 1999).

The combination of these studies raises the possibility that the amygdala is necessary for the acquisition of sufficient emotional knowledge to allow later emotion

recognition, but is not needed for 'on-line' emotion recognition. This hypothesis is in line with the findings we noted in the previous chapter for emotional enhancement of memory (Shaw, Brierley et al. 2005). However, it should be noted that several case reports of patients who acquired bilateral amygdala damage adulthood found deficits in emotion recognition-particularly for fear- (Calder, Young et al. 1996; Broks, Young et al. 1998). Additionally a re-analysis of the original data from the patients in the Hamann study suggested that there were subtle recognition deficits in the patients previously reported as intact (Schmolck and Squire 2001). As mentioned earlier, there are also some problems arise in estimating age of damage to the amygdala in several of these case reports. For example, some patients have a history of seizures from childhood, which may have compromised the amygdala early in development, and then proceeded to operative excision in adulthood. Whether the key damage is in childhood or adulthood is difficult to gauge from patients with complicated clinical and neurosurgical histories.

Table 4.1 A review of case studies of subjects with bilateral amygdala damage and associated deficits in emotion recognition.

Ref.	Patient	Left amygdala	Right amygdala	Other	Aetiology	Emotional categories with abnormal forced choice labeling	Emotional categories showing abnormal ratings
1,2	SM	Complete	Complete	None	Urbach-Wiethe	Fear	Fear, Anger, Surprise
2	DR	Partial (25%)	Minimal (4%)	Minimal	Surgical	Fear, Anger, Disgust	Fear, Angry, Sad, Disgust, Surprise
2,3	EP	Complete	Complete	Extensive	Encephalitis	Fear, Sad	Angry
2,3	GT	Complete	Complete	Extensive	Encephalitis	Fear, Anger, Disgust (sad in force choice)	Surprised
4	GP	Complete	Complete	Extensive	Encephalitis	Fear, Sad, Anger, Disgust	-
2,5	SE	Complete	Complete	Extensive	Encephalitis	Fear	Surprised
2, 7	SP	Gliosis	Complete	Moderate	RTL and L sided gloisis	-	Fear, Sad, Disgust
8	NM	Partial	Complete		Infarct and gloisis	Fear, Sad	
2, 9	JM	Complete	Complete	Extensive	Encephalitis	-	Fear, Sad, Disgust, Anger
2, 9	RH	Complete	Complete	Extensive	Encephalitis	-	Angry
2, 10	DBB	Complete	Partial	None	Surgical treatment for intractable aggression	-	None
11	JC	Partial	Extensive	Extensive	Encephalitis	Fear, Anger, Sad, Happy	-
11	YW	Partial	Virtually complete	Extensive	Encephalitis	Fear	-
11	RB	Complete	None	Moderate	Encephalitis	Fear	-
12	Bilat1	Not specified- 'focal'	Not specified	Not specified		Fear, Disgust- relative to healthy control only, not other brain lesion controls	-
12	Bilat2	Not specified	Not specified	Not specified	Not specified	Fear and disgust.	
13	HY	Total	Total	Extensive medial temporal	Encephailitis	Fear (taken as happiness)	-
14	CB	Sclerosis	Sclerosis	Proceeded to R ATL aged 22	Mesial temporal sclerosis; onset 7 yo	Intact	-
14	JC	DNET	Sclerosis	Proceeded to L ATL aged 25	Onset epilepsy age 12	Disgust, Anger	-
14	CH	Sclerosis	Sclerosis	Dilated ventricles, and some general atrophy	Encephalitis as a child and febrile convulsions	Happy, fear, sad, disgust, anger	-

1. (Adolphs R, et al 1995); 2. (Adolphs R, et al., 1999); 3. (Hamann et al 1996); 4. (Schmolck H & Squire LR, 2001); 5 Calder AJ et al 1996 7. (Anderson AK & Phelps EA, 2000); 8. (Sprengelmeyer R, et al., 1999); 9.Adolphs R et al. 1998 ; 10 Lee GP et al. 1998; 11 (Broks et al 1998) 12 (Rapcsak et al 2000); 13 (Sato et al 2002); 14 (Brierley et al 2004)

Efforts to define the effects of unilateral amygdala damage have largely rested on studies on patients with mesial temporal lobe epilepsy, many of whom have proceeded to surgical treatment of epilepsy, typically with excision of the anterior temporal lobe. The size of these studies allows systematic investigation of the impact of developmental, with the age of onset of epilepsy usually taken as the age of the onset of damage to the amygdala. The limitations of this approach have been discussed earlier. Four studies have reported that an earlier age of onset of seizures is associated with greater deficits in the recognition and/or rating of emotions, particularly fearful faces (listed in Table 4.2 over), although there is also a negative finding (Brierley, Medford et al. 2004). In the studies reporting an association with age of onset of epilepsy, it is of note that only subjects with right sided amygdala damage showed this developmental effect suggesting an interaction of the side and stage of amygdala damage.

A final issue concerns the range of basic emotional stimuli that are processed by the amygdala. At one extreme, some have posited that the amygdala is dedicated to the processing of fear or stimuli which signal potential threat, mainly supported by studies of subjects with bilateral selective lesions of the amygdala(Adolphs, Tranel et al. 1994; Adolphs, Tranel et al. 1999). The amygdala has also been held to process signals of distress (fear and sadness)(Blair, Morris et al. 1999) or environmental ambiguity (fear and surprise)(Whalen, Shin et al. 2001). Others argue explicitly for lateralisation of processing, with the right amygdala processing negative basic emotions, which would typically evoke withdrawal behaviour (fear, sad and disgust) (Anderson, Spencer et al. 2000). This division was originally suggested on the basis of neurophysiological studies among healthy subjects and in its original form held that

Table 4.2. Group studies examining the effects of unilateral amygdala damage on emotion recognition.

Reference	L ATL	R ATL	Aetiology	Emotional categories with abnormal forced choice labeling	Emotional categories with abnormal ratings	Relationship to age of onset of epilepsy?
Adolphs et al. (2001)	15	0	TLE (surgical) / encephalitis	N/A	Normal	For fear only: Spearman r=.47 (p=.15)
	0	11	TLE (surgical) / encephalitis	N/A		For fear only: Spearman r=.40, (p=0.3)
Anderson et al (2000)	11	0	TLE – surgical	N/A	Normal	Not given
	0	12	TLE – surgical	N/A	Sad and disgust	Pearson's r=.54, p<0.01
Brierley et al (2004)	14	0	TLE – surgical	Fear, disgust	N/A	(Spearmans. rho=0.38, p=0.16)
	0	18	TLE – surgical	Fear, disgust, anger and surprise	N/A	Spearman's rho=-0.03, p=0.89
Meletti et al (2003)	31	0	Mesial temporal sclerosis (N=16) and focal lesions (N=15, of which 2 involving amygdala)	Normal	N/A	Spearman's r=-.25, p>0.05
	0	32	Mesial temporal sclerosis (N-17) and focal lesions (N=15, of which 8 involve amygdala)	Fear (mesial temporal sclerosis group with early onset seizures). Focal amygdala lesions not associated with impairment.	N/A	Spearman;s r=.64, p<0.01
(Mc Clelland, Garcia et al. 2006)	0	12	ATL. Early onset seizures <6y (N=5) compared with late onset (N=7).	Fear only(used face-matching task)	N/A	Early onset only impaired (group comparisons only given-no age of onset correlations are possible)

the left hemisphere processes emotions linked to approach behaviours- happy, surprise and anger- although this corollary component has not been supported in amygdala lesion studies(Davidson 1992; Davidson 1993; Mandal, Borod et al. 1999). At the other extreme, researchers have argued for greater breadth for affective processing by the amygdala as bilateral damage arising from UW disorder has been

associated with compromised processing of all the basic emotions (fear, sad, happy, disgust, surprise and anger)(Sato, Kubota et al. 2002; Siebert, Markowitsch et al. 2003).

We thus aimed to study the effects on facial emotion recognition of amygdala lesions arising from pathologies sustained at distinct developmental stages. Thus our 'early' amygdala damage group have relatively focal pathology of the amygdala stemming mainly from a congenital non-progressive tumour which arises in early childhood. This group is compared with subjects in whom damage to the amygdala arose as a consequence of surgery in adulthood. We had hoped to explore laterality effects in the study, paying particular attention to possibility of interaction with the stage of amygdala damage. However, there was a preponderance of patients with right sided damage in the late amygdala damage group which limited our examination of such effects. We include a comparison group of subjects with similar clinical histories of chronic epilepsy and medication exposure, to ensure deficits are not due to factors related to the illness and its associated treatment and disability (Rapcsak, Galper et al. 2000).

Although the focus of this study is the visual modality there is evidence that the amygdala may also be important for auditory affective processing. Thus some, though not all, studies of patients with bilateral amygdala damage have shown impairments in the recognition of expressions of fear, not only in the face, but also in the voice (Scott SK, et al., 1997) (Sprengelmeyer R, et al., 1999 (Adolphs R & Tranel D, 1999) (Anderson AK & Phelps E, 1998). Functional MRI has also detected amygdala activation during both facial and vocal expressions of fear in healthy subjects (eg .see Phillips ML, et al., 1998). Similarly lesion studies also suggest the

amygdala is important in olfaction (Siebert, Markowitsch et al. 2003), and functional imaging work has demonstrated that the amygdala is activated by the affective properties of odours (Royet, Hudry et al. 2001; Zald 2003) although the relationship between these findings and social behaviour is unclear in humans. So while acknowledging that there is evidence that the amygdala may be a multi-modal processor of affective material, we focus only on a visual recognition paradigm.

4.3 Hypotheses

We hypothesize that there will be an effect of developmental stage of damage of the amygdala on the recognition of facial expressions of the basic emotions. Specifically, we predict that early onset amygdala lesions will be associated with greater impairment in the recognition and evaluation of the basic emotions. Secondly we predict that subjects with right sided damage may be more impaired in emotional recognition. Finally we examine the range of emotional expressions that are affected by amygdala damage.

4.4 Methods

4.4.1 Participants.

1) Early (focal) lesions of the amygdala. Sixteen subjects with focal lesions of the right amygdala (N=6) or left amygdala (N=10), thought to arise from a congenital lesion as described earlier.

2) Late amygdala damage. Nine subjects in the late amygdala damage group had surgical excision of a normal amygdala in adulthood. Only one subject had a left sided excision.

3) Clinical controls. Fourteen subjects with focal lesions sparing the amygdala, in the temporal (N=9), or neighbouring parietal lobes (N= 2), or insula (N=1). Four had right sided and nine had left sided lesions. These lesions were also predominately low grade tumour or vascular abnormalities.

4) 46 healthy controls with no history of mental or progressive neurological disorders.

4.4.2 Tasks.

Standard neuropsychometry. To determine IQ, the clinical groups completed subtests of the Wechsler Adult Intelligence Scale-III (for verbal IQ the vocabulary, digit span, comprehension and similarities subscales, for performance IQ the block design and object assembly subscales.) For the neurologically intact control subjects an estimate of IQ was obtained from the National Adult Reading Test (Nelson 1982). All clinical subjects also completed the Benton Facial Recognition task which requires the matching of faces of identical individuals taken under different levels of illumination and at different angles(Benton, Sivan et al. 1983).

Experimental tasks. Ekman and Freisen series of pictures of facial affect were used in the experimental task (Ekman 1976).

Labeling task. Six faces portraying each of six basic emotions were presented in randomized order and subjects were asked to choose which one of the six basic emotional terms best matched the facial expression. The terms were presented below each face. Subjects completed the task at their own pace.

Intensity rating task. Four of the six identities (two male and two female) portraying all six of the basic emotions were then presented. As each of the 24 faces was presented subjects were asked to rate the intensity of one of the six basic emotion terms (sad, happy, surprise, anger, fear, disgust). The rating scale was presented below the face and ranged from 1 (not at all) to 10 (very much). After rating all faces on this emotional term, the faces were again presented and the subjects asked to rate the intensity of the face with respect to a new emotional term. Thus in total the subjects were presented with each of the 24 faces on six occasions.

4.4.3 Analysis

To explore the effects of stage of damage on the forced choice labeling of emotions, a repeated measures ANOVA was conducted with the category of emotion as the within subject factor and group (early or late damage amygdala groups, clinical and healthy controls) as the between group factor. Interactions of category of emotion and group were explored by one-way ANOVAs for each emotional category. Pairwise post hoc contrasts were made with the Bonferroni correction applied for multiple comparisons.

To explore the effects of right and left sided focal amygdala damage the early amygdala damage group were split into left and right damage. There was only one subject in the late amygdala damage group with left sided damage and thus it was not possible to explore the effects of side of damage in this group, and the right and left sided damage patients were combined. For this reason it was also not possible to explore the interaction of side and stage of amygdala damage. For these analyses non-parametric statistics were used given small group sizes.

The analysis proposed by Schmolck and Squire was used for the ratings task (Schmolck and Squire 2001). The ratings given for each face to its 'correct' label (the

rating for the emotional label 'sad' given in response to each sad face) was defined as the congruent rating. The mean of all the ratings given in response to the same face for the 'incorrect' labels (i.e. for a sad face, the mean of the responses given to the labels 'happy/frightened, surprised etc') was taken as the incongruent rating. A discrimination index was calculated as the difference between the congruent and incongruent ratings. A high discrimination index means that the individual sees a face as its prototype rather than resembling the other basic emotions (thus the 'sad' face is not seen as containing nuances of happy, surprised, disgusted, angry or fearful expressions). A low discrimination index implies that the individual sees, for example, the prototypically sad face as being less distinctly 'sad' and resembles happy, sad, angry, fearful and surprised expressions.

In addition for each emotional category the mean ratings for all of the six basic emotional labels were calculated (thus for the four sad faces, there were six mean values, one for each of the six basic emotional category terms). To compact the large amount of data, cluster analysis was used, as described in (Anderson and Phelps 2000). The average ratings for each emotional category were transformed with a Euclidean distance metric and the hierarchical solutions were observed using a between-groups linkage algorithm (all analyses were conducted using SPSS 14). In these hierarchical diagrams expressions which are judged most similar form clusters at the bottom of the tree, and emotions that are seen as dissimilar from clusters near the top of the tree. This allows a qualitative examination of the degree to which each group viewed a 'sad' face as also resembling the other basic emotional categories.

Possible moderating variables such as estimated IQ, duration of seizures, and general face processing ability were examined, initially by correlations, and if significant, treated as covariates in the repeated measures ANOVA.

4.5 Results

Demographic and neuropsychological details are given in table 4.3. There were no significant differences between the groups in age, duration of epilepsy or performance on the Benton Facial Recognition test in the clinical groups. All clinical groups had a significantly lower IQ than the healthy controls, but did not differ from each other.

Table 4.3 Demographic and clinical characteristics of participants.

	Early amygdala	Late amygdala	Clinical controls	Healthy controls	Significance
Gender M/F	7/9	5/4	7/8	18/28	X^2=.98, p=.81
Age (mean SD)	33 (10)	36 (10)	30 (7)	33 (10)	F(3,78)=.85, p=.47
IQ (mean SD)	99 (15)	98(16)	91 (14)	111 (8)	F(3,78)=13.1, p<.001, All clinical groups < NV (P<.01)
Handed R/L	15/1	8/1	13/2	41/5	X^2=.45, p=.93
Side of damage R/L	6/10	8/1	4/11	-	χ^2=9.8, p=0.008
Duration of epilepsy Mean (SD)	20 (15)	17 (12)	11 (8)	-	F(2,37)=2.6, p=0.09
Benton Facial recognition test	44 (4)	45 (3)	43 (5)	-	F(2,32)=.43, p=.66

4.5.1 Labeling task

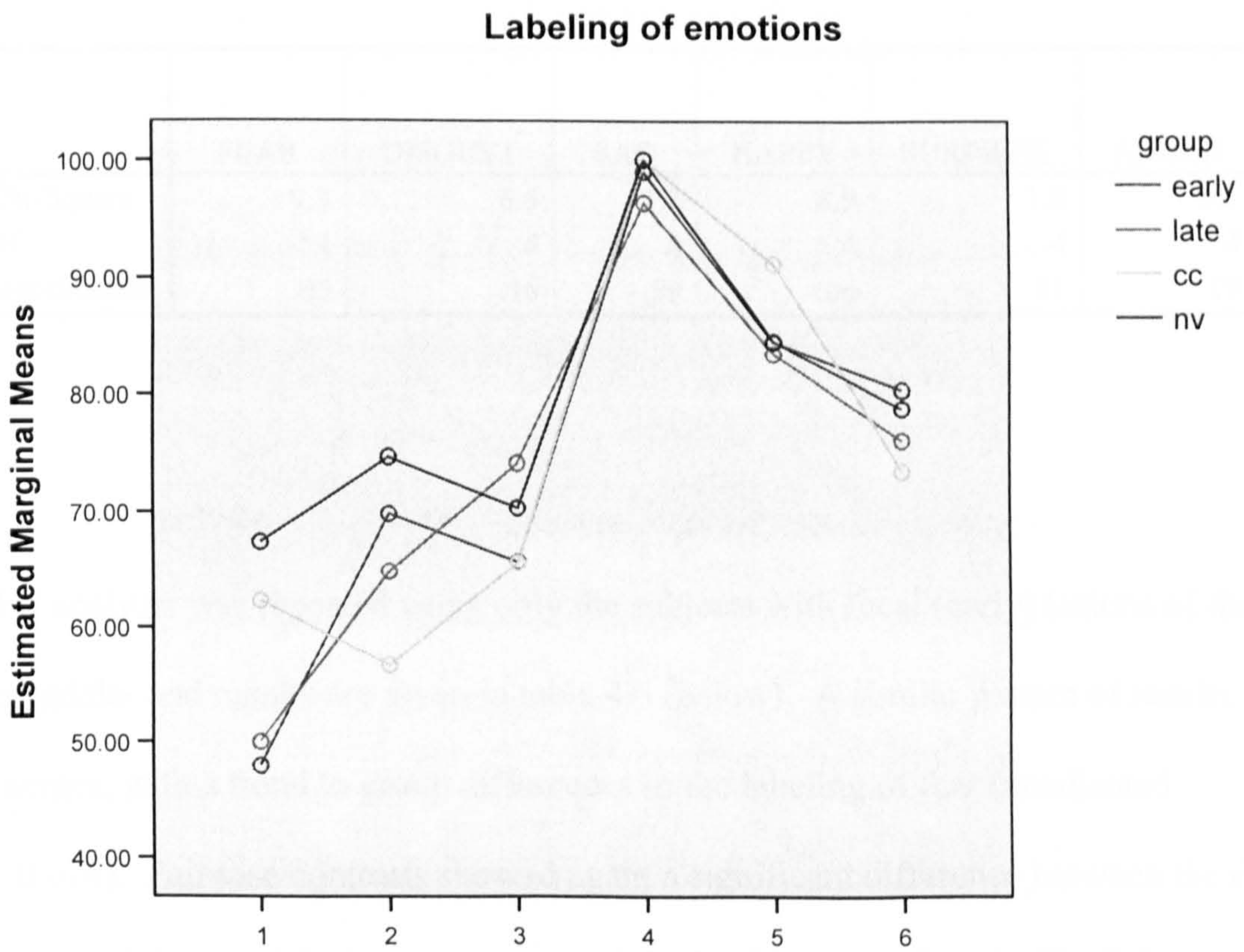
The number of correct responses in the forced choice labeling task for each emotional category was entered as a within subjects measure with the group as the between subjects factor in a repeated measures ANOVA.

Table 4.4: Mean correct labeling score (mean % and SD) for each group by individual emotions

	Group	Mean	Std. Deviation
FEAR	Early amygdala	47.9	27.8
	Late amygdala	50.0	27.6
	Clinical control	62.2	24.7
	Healthy control	67.3	22.4
DISGUST	Early amygdala	69.7	24.5
	Late amygdala	64.8	28.1
	Clinical control	56.6	26.5
	Healthy control	74.6	19.1
SAD	Early amygdala	65.6	19.6
	Late amygdala	74.0	26.4
	Clinical control	65.5	23.9
	Healthy control	70.2	17.5
HAPPY	Early amygdala	98.9	4.1
	Late amygdala	96.2	7.3
	Clinical control	100.0	-
	Healthy control	100.0	-
SURPRISE	Early amygdala	84.3	25.4
	Late amygdala	83.3	18.6
	Clinical control	91.1	10.6
	Healthy control	84.4	19.3
ANGER	Early amygdala	80.2	24.5
	Late amygdala	75.9	16.8
	Clinical control	73.3	16.4
	Healthy control	78.6	19.1

There was a main effect of category of emotion, ($F(5,410)=40$, $p<0.001$, Greenhouse-Geisser corrected) with the order of overall correct recognition being happiness (mean percentage correct 99%); surprise (86%), anger (77%), sad (69%), disgust (66%) and fear (57%). There was no significant effect of group ($F(3,82)=1.7$, $p=0.17$): the order of groups was healthy control (mean percentage score 79%, SD 9%), clinical controls (mean 74% SD13), early amygdala damage (mean 74%, SD 9) and late amygdala damage group (mean 73%, SD10). There was no significant interaction of group with category of emotion ($F(15,410)=1.65$, $p=0.07$, Greenhouse Geisser corrected).

Figure 4.1 : Scores for correct labeling of emotions for each group.



Key 1=fear; 2=disgust; 3=sad; 4=happy; 5=surprise; 6=anger
EA=early amygdala; LA=late amygdala; cc=clinical controls; NV=healthy controls.

Kruskal Wallis tests were used to examine the effects of side of amygdala damage, comparing the overall accuracy scores of the right or left amygdala damage groups, initially combining both the early and late damage groups. Comparisons were made with the left clinical, right clinical and healthy controls. There was no effect of group on overall score, although a significant group difference was found in the forced choice labeling of fear- Table 4.5. In pairwise contrasts, the right amygdala damage group were impaired relative to the healthy controls only ($Z=-2.8$, $p=.005$, Bonferroni corrected $p=0.05$). There were no other significant pairwise differences.

Table 4.5. Kruskal Wallis test comparing left amygdala (both late and early damage combined), right amygdala (both early and late damage combined), left clinical controls, right clinical controls and healthy controls.

	FEAR	DISGUST	SAD	HAPPY	SURPRISE	ANGER	TOTAL
Chi-Square	9.3	6.5	2.8	8.9	1.6	6.1	5.8
Df	4	4	4	4	4	4	4
Significance	.05	.16	.59	.06	.81	.19	.21

This analysis was repeated using only the subjects with focal (early) lesions of the amygdala- and results are given in table 4.6 (below). A similar pattern of results emerges, with a trend to group differences in the labeling of fear (unadjusted $p=0.074$). Pairwise contrasts showed again a significant difference between the right focal (early) amygdala damage group and the healthy controls only ($Z=-2.5$, unadjusted $p=0.01$) which did not survive a Bonferroni correction for multiple comparisons. . In summary there was no evidence that the effects of amygdala

Table 4.6 Kruskal Wallis test comparing left amygdala (early damage only), right amygdala (early damage only), left clinical controls, right clinical controls and healthy controls.

	FEAR	DISGUST	SAD	HAPPY	SURPRISE	ANGER	TOTAL
Chi-Square	8.5	5.2	2.2	5.4	2.8	5.7	6.9
df	4	4	4	4	4	4	4
Significance.	.07	.25	.69	.24	.58	.22	.14

damage were dependent on the developmental stage at which damage was acquired. Subjects with damage to the right amygdala (either late or early) appeared to have the most pronounced deficits in forced choice labeling, although differences reached significance only in comparisons with healthy controls.

4.5.2 Intensity ratings.

Three subjects in the early amygdala group, five in the clinical control and five in the healthy control group did not complete this demanding task.

The mean ratings for the congruent (values given to the 'correct' labels for each facial expression and label) and incongruent ratings (values given to the 'incorrect' labels) averaged across all emotions for each of the groups is shown in table 4.7. The groups did not differ in the congruent ratings (i.e. all groups gave the same intensity ratings for the 'correct' label for each emotion). The groups did however differ in the incongruent ratings, with all three clinical groups giving higher mean ratings than the healthy controls (all $p<0.01$, Bonferroni corrected).

Table 4.7 Mean congruent and incongruent ratings (with standard deviations) by group for all six basic emotional expressions combined.

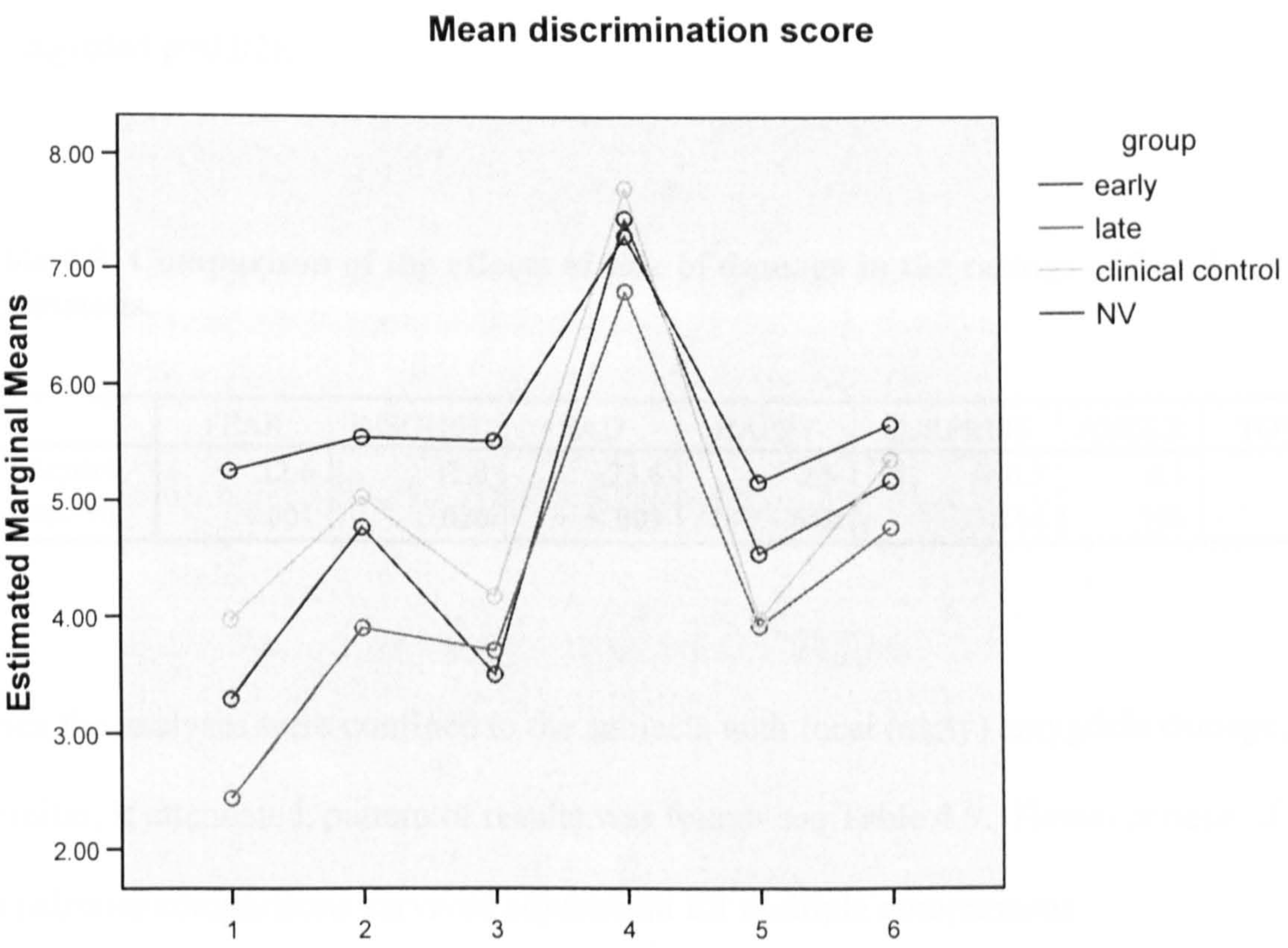
	Early amygdala	Late amygdala	Clinical controls	Healthy controls	Test of significance
N	13	10	9	41	
Congruent ratings	8 (1.3)	7.9 (1.4)	8.6 (0.9)	7.9 (1.3)	F(3,69)=0.7, p=0.55
Incongruent ratings	3.2 (0.9)	3.6 (1.5)	3.6 (1.1)	2.2 (0.8)	F(3, 69)=10.1, p<0.001

To explore the results further, the discrimination scores (congruent-incongruent ratings) for each category of emotion was entered as a within subjects factor in a repeated measures ANOVA, with group as a between subjects factor. There was a significant main effect of category of emotion, ($F(5,345)= 50$, $p<0.001$), and group ($F(3,69)=4.3$, $p=0.008$). Post hoc tests with Bonferroni correction showed that the late amygdala damage group had a significantly smaller overall discrimination index for all the emotions combined than the healthy controls (adjusted $p=0.02$). The difference between the early amygdala damage group and healthy control did not survive adjustment for multiple comparisons (adjusted $p=0.15$). There was a significant interaction ($F(15,345)=2.53$, $p=0.003$, Greenhouse Geisser corrected)- shown below in Figure 4.2. This was explored by one-way ANOVAs for each emotional category.

In the one-way ANOVAs, there were overall significant group differences in the discrimination index for the emotional categories of fear ($F(3,69)=9.2$, $p<0.001$) and sadness ($F=7.9$, $p<0.001$). For both emotions the early and late amygdala groups had

a significantly smaller discrimination index than the healthy controls only ($p<0.01$, Bonferroni corrected).

Figure 4.2 Mean discrimination scores for each group in the rating of the intensity of facial expressions of emotions.



Key 1=fear; 2=disgust; 3=sad; 4=happy; 5=surprise; 6=anger
EA=early amygdala; LA=late amygdala; cc=clinical controls; NV=healthy controls.

In line with previous analyses we examined laterality effects by combining subjects with early and late amygdala damage, and splitting this amygdala damage group into those with right or left sided damage. Comparisons were with the right and left sided

damage clinical controls and healthy controls. The significant group differences for fear, disgust and sadness were explored with Mann-Whitney U tests- Table 4.8. The right amygdala damage group were impaired relative to the healthy controls in the ratings of fear (p=0.001), sadness (p=0.005) and disgust (p=0.03, all Bonferroni corrected). The only other pairwise contrast that survived Bonferroni adjustment was the rating of sadness in the left clinical controls group relative to healthy controls (Z=-2.9, adjusted p=0.02).

Table 4.8 Comparison of the effects of side of damage in the ratings of facial expressions.

	FEAR	DISGUST	SAD	HAPPY	SURPRISE	ANGER	TOTAL
Chi-Square	22.6	11.0	23.6	2.5	6.7	6.1	14.2
Asymp. Sig.	<.001	.026	<.001	.642	.154	.193	.007

When the analyses were confined to the subjects with focal (early) amygdala damage, a similar, if attenuated, pattern of results was found- see Table 4.9. However none of the pairwise comparisons survived adjustment for multiple comparisons.

Table 4.9 Comparison of the effects of side of damage in the ratings of facial expressions, excluding participants with late amygdala damage.

	FEAR	DISGUST	SAD	HAPPY	SURPRISE	ANGER	TOTAL
Chi-Square	12.9	8.4	17.2	2.0	4.9	2.9	8.9
Asymp. Sig.	.01	.08	.002	.73	.29	.56	.06

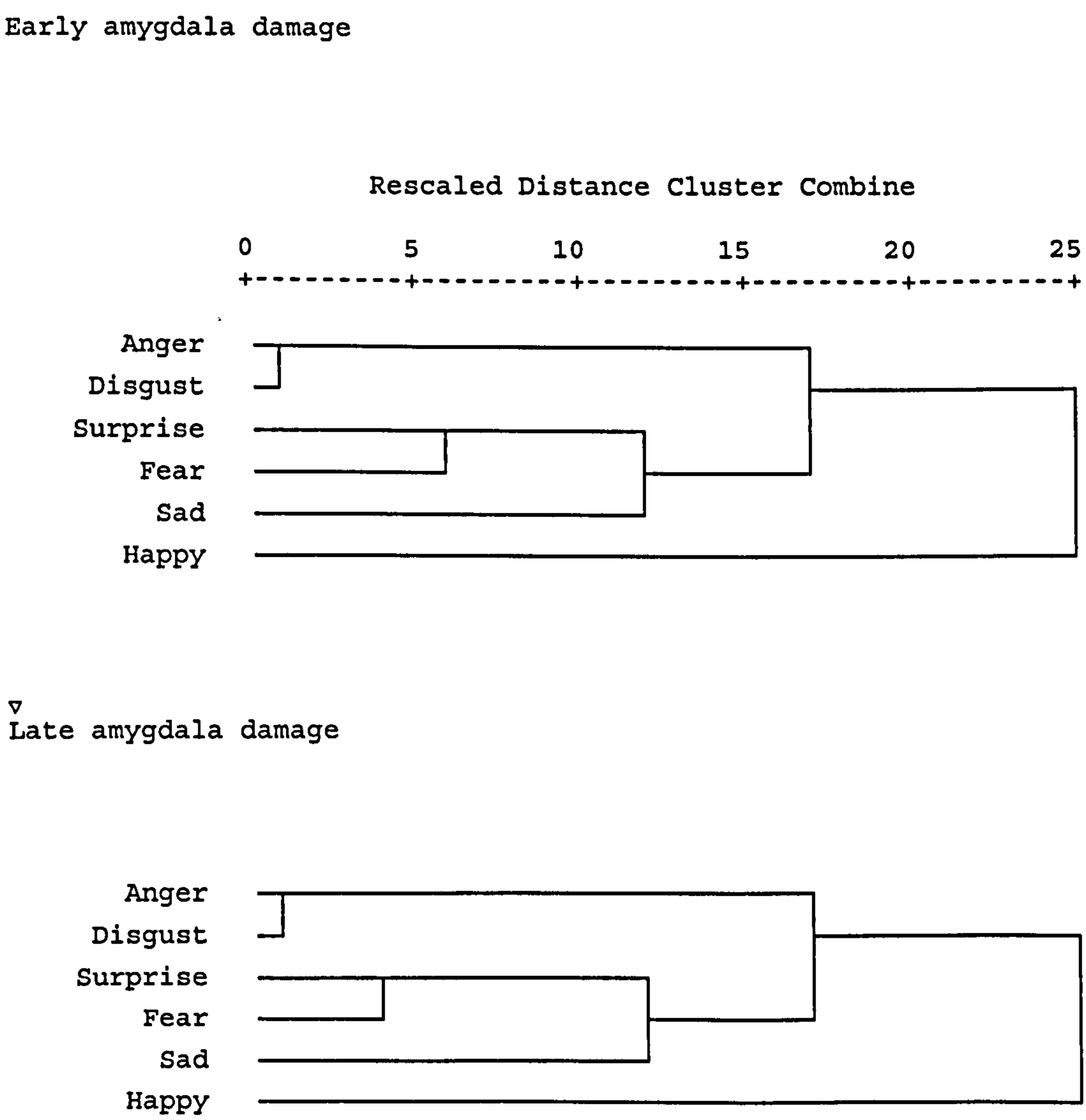
4.5.3 Effects of possible moderating variables.

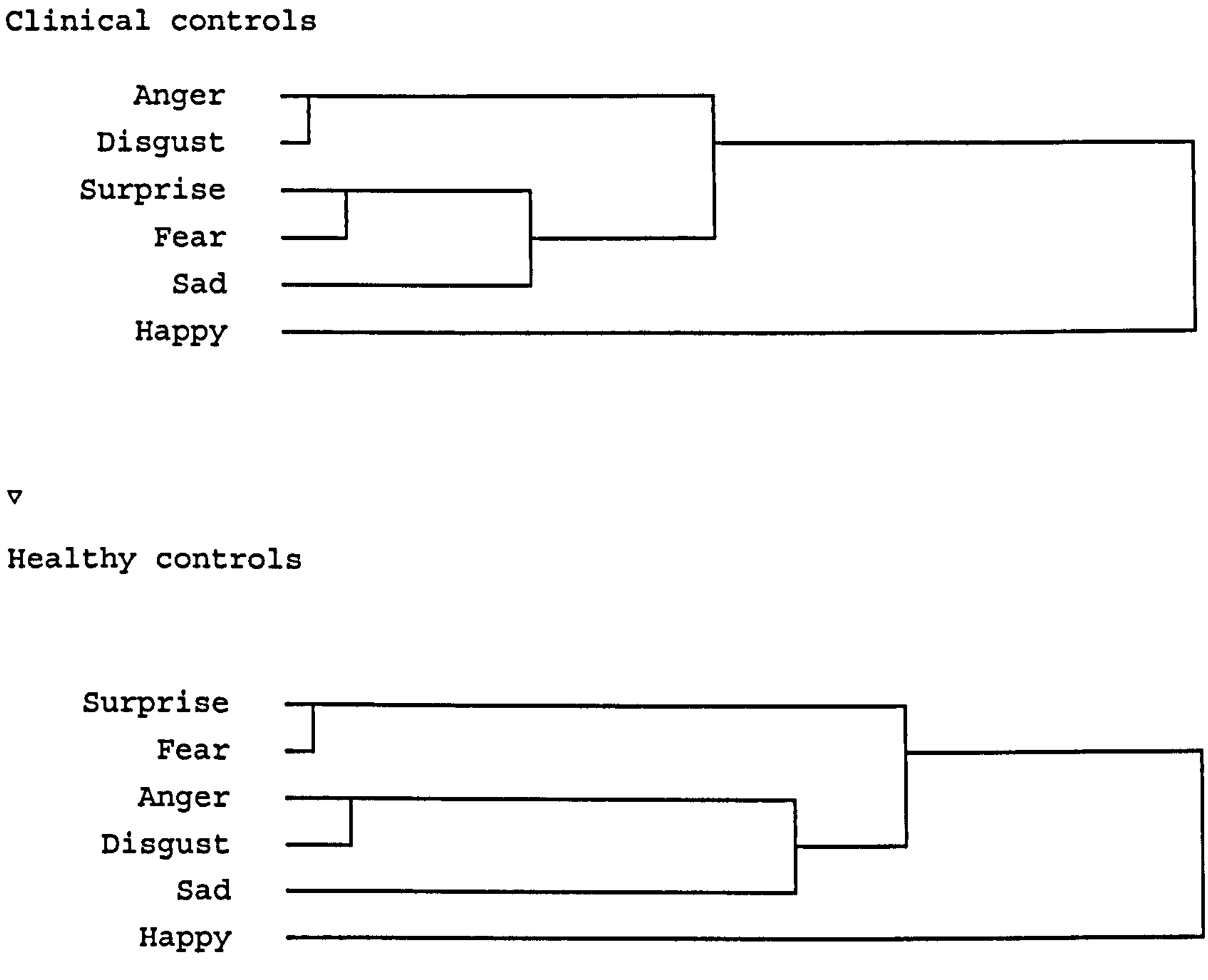
There were no significant differences between the clinical groups in the Benton Facial Recognition task. In addition, correlations between the mean overall discrimination index and the Benton Facial Recognition task scores were not significant (Pearson's r=0.08, p=0.66). IQ differed between groups and was also correlated significantly with overall discrimination index (r=0.32, p=0.008). Entering IQ as a covariate however in the analyses did not alter the pattern of results: the late amygdala group remained significantly impaired (with a smaller discrimination index) relative to the healthy controls (p=0.013). The significant interaction of group and emotion remained with IQ as a covariate (F=2.14, p=0.01) and still arose due to impairment in the early and late group in the discrimination of fear and sadness (all p<0.01, Bonferroni adjusted) relative to healthy controls only. There was no significant correlation between duration of epilepsy (r=-.17, p=.40) or age (rho=-0.07, p=0.71) and the discrimination index.

4.5.4 Hierarchical trees

Separate hierarchical tree solutions were generated as described earlier for each group to illustrate the judgment of similarity between distinct emotion types- see figure 4.3 over.

Figure 4.3 Hierarchical tree solutions (dendograms) illustrating the similarity in ratings between the basic emotional expressions. Emotional categories judged as more similar join near the bottom of the tree.

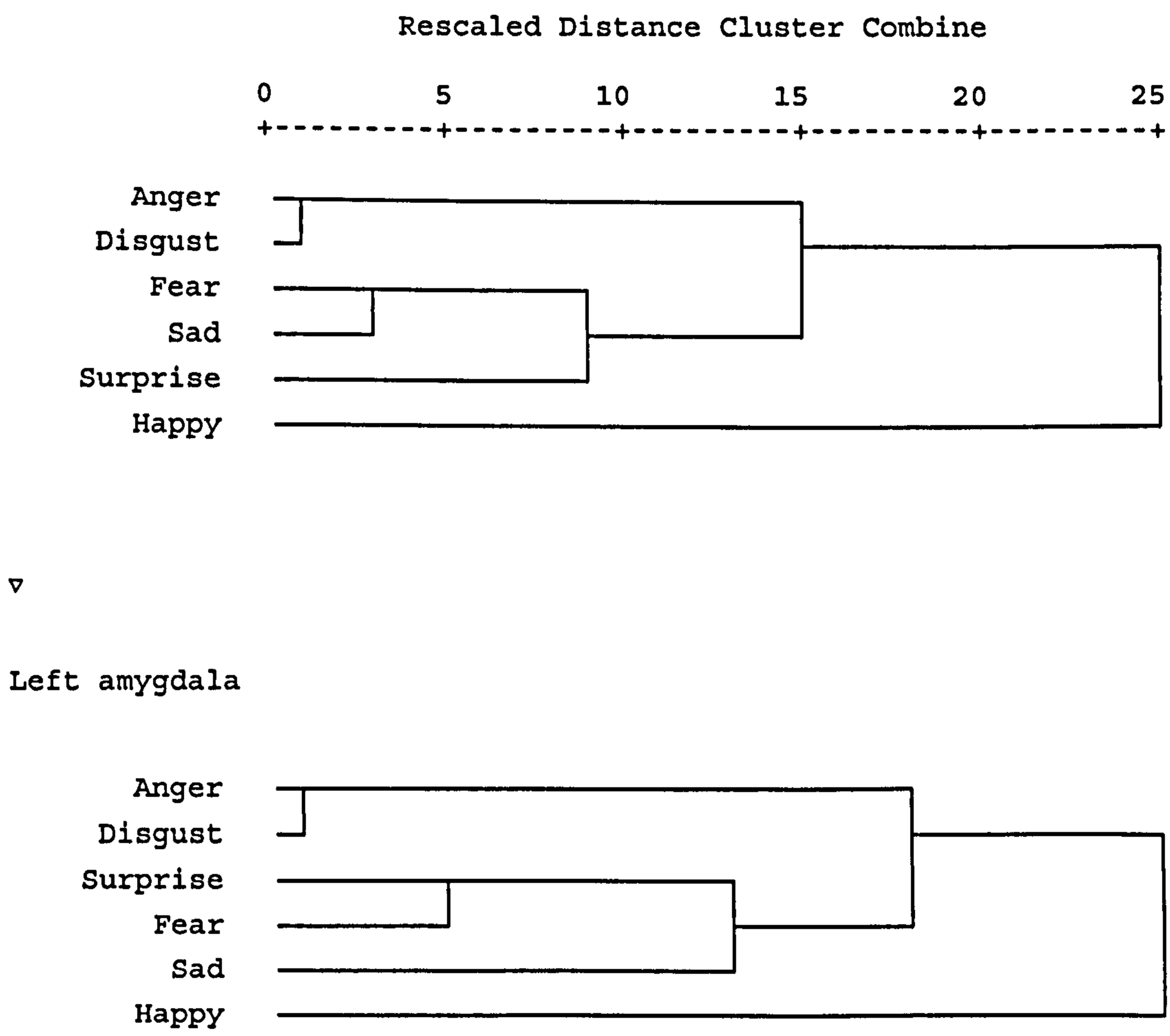




As can be seen, there was a marked consistency in how all the clinical groups perceived the overlap between the difference facial emotions. Facial expressions of sadness were rated as similar to fear and surprise by all these groups, whereas the healthy controls rated the sac expressions as more similar to disgust and anger

For analyses of laterality, the clinical group was collapsed in view of the small numbers. Separate trees were thus derived for right amygdala damage (early and late), left amygdala damage (early and late), clinical controls (shown above in Figure 4.3) and healthy controls (shown above in Figure 4.3).

Figure 4.4 Hierarchical tree solutions (dendograms) illustrating the similarity in ratings between the basic emotional expressions for the right and left amygdala damage groups



The right amygdala damage group rated faces in an abnormal fashion, giving ratings which indicated a very high degree of perceived similarity between sad and frightened facial expressions. Indeed the right amygdala group rated fear as being more similar to sadness than surprise- a very abnormal pattern. The left amygdala damage group showed a very similar pattern of ratings to the clinical controls.

4.6 Discussion.

4.6.1 Summary.

The results did not support our hypothesis that subject with early amygdala damage would show greater impairment in labeling and rating the intensity of facial expressions of emotion. Indeed there was a suggestion that subjects with late amygdala damage had more difficulty in discriminating one emotion from another. The group differences were most apparent when an intensity rating task was used, rather than in the forced choice labeling paradigm. Other studies have reported intact forced choice labeling but abnormal intensity ratings of emotional expressions(Adolphs and Tranel 2004) and the discrimination index has proved a highly sensitive method for detecting subtle impairments(Schmolck and Squire 2001).

Subjects with right sided amygdala damage alone showed significant impairment relative to healthy controls in the discrimination of emotions. This was reflected in significantly impaired forced choice labeling of fearful expressions and the tendency to view frightened and sad faces as similar, in marked contrast to the viewing of fear and surprise as similar shown by left amygdala, clinical and healthy controls. This suggests that the right amygdala is particularly important in attaining perceptual clarity for facial expressions of fear,

4.6.2 The developmental dimension.

The finding of abnormal ratings of emotional expressions in subjects with either early or late damage to the amygdala is in keeping with a role for the amygdala in the 'on-line' recognition of emotions. It does not support the hypothesis that the amygdala is

necessary only for the acquisition of sufficient emotional knowledge to allow accurate emotional recognition in later life. It should be stressed that the results do not rule out a role for the amygdala in the acquisition of knowledge and experience necessary for emotion recognition in addition to its role in the 'on-line' recognition of emotions. However, if the amygdala is necessary both for the acquisition of a skill and its performance then equal, if not greater deficits, would be expected among those with earlier damage. This was not found: indeed the late amygdala damage group were most impaired in terms of their ability to discriminate between the emotional expressions, although there were no significant differences between the early and late amygdala damage groups.

There are several caveats to consider. Firstly, the differences in labeling and rating of emotions were significant only when comparison was made with healthy controls and not subjects who had focal lesions which spared the amygdala. To this extent it could be argued that the study does not give definitive evidence for a specialized role in emotional recognition for the amygdala. However, as the clinical controls did not differ significantly from healthy controls, the overall pattern of results suggests a particularly important role for the amygdala in emotion recognition and evaluation. Affective processing is likely to involve a distributed network of regions, and even though the amygdala maybe a key component, the effects of damage to any one part of the system are likely to have subtle effects. Some of the clinical controls had lesions in regions such as the somatosensory cortices, which may play a key role in emotion recognition(Adolphs, Damasio et al. 2000). Thus the lack of significant difference from clinical controls may reflect both a lack of power to detect small

effects, and compromise in the clinical control group to other components of the emotion recognition system.

The late, but not early, amygdala damage group was significantly different from healthy controls in the mean discrimination index, showing impairment in the ability to distinguish between emotional expressions. This may in part reflect the more extensive damage in the late amygdala damage group, which arose from surgical excision of the anterior temporal lobe, a region that may be important in emotion recognition. Intracranial single cell recordings demonstrate that cortical regions adjacent to the amygdala such as the entorhinal cortex, and subcortical structures such as the hippocampus respond to facial expressions of emotion (Ojemann, Ojemann et al. 1992; Fried, MacDonald et al. 1997). We note however that the pattern of results from the subjects with more focal (and early) damage to the amygdala was very similar to those of the combined amygdala damage groups, suggesting that the amygdala is indeed the pivotal structure. This is a significant finding as previous studies into the effects of unilateral amygdala damage have typically used patients with extensive surgical damage to the anterior and medial temporal lobe and had varying degrees of damage to the amygdala itself (Anderson, Spencer et al. 2000; Adolphs, Tranel et al. 2001; Boucsein, Weniger et al. 2001; Brierley, Medford et al. 2004). Indeed, Adolphs et al reported only a weak correlation between the extent of amygdala damage and the deficits in emotion perception(Adolphs, Tranel et al. 2001). Another study of a small number of patients with focal lesions incorporating the amygdala did not find the patients to be severely impaired in the recognition of emotions, unlike patients who had more diffuse mesial temporal lobe sclerosis(Meletti, Benuzzi et al. 2003). Thus our demonstration of impairments in the

labeling and evaluation of basic emotional expressions in patients with relatively focal amygdala lesions is of some significance.

4.6.3 Laterality effects.

There was evidence of laterality in affective processing with the lesions of the right amygdala associated with more pervasive impairments in processing emotions. This is in keeping with the majority of lesion studies which report a right hemispheric bias in affective processing, although to our knowledge this is the first study to demonstrate this laterality in a sample which includes subjects with focal, non-operative lesions of the amygdala.

4.6.4 Range of emotional categories affected by amygdala damage.

The finding of impaired discrimination of fear and sadness in subjects with right amygdala damage may seem to run counter to the findings of specific deficits in the recognition of fear alone among the basic emotions in patients who have bilateral damage. However, as mentioned earlier, of the 14 reported case studies of people with bilateral amygdala damage, there were only two who showed deficits that were specific to fear stimuli (Fine and Blair 2000). Interestingly, around half of subjects with bilateral amygdala studied, were also found to have abnormal recognition on forced choice labeling or ratings of sad facial expressions (Fine and Blair 2001). In a large study of nine patients with bilateral amygdala damage due to Urbach-Wiethe disease, the most anomalous of all ratings were the high scores given by patients in rating how afraid a sad face looked(Siebert, Markowitsch et al. 2003). The deficits in the evaluation of fear and sadness we demonstrate is compatible with the model of the amygdala as processing signal of distress (Blair, Morris et al. 1999). Thus damage to

the amygdala may disrupt a critical component of the circuitry regulating social interactions.

Our data indicate anomalous ratings of expressions of disgust also in subjects with right sided amygdala damage. The overlap with the findings of Anderson and colleagues is striking: using an identical rating paradigm they reported deficits in the rating of expressions of fear, sadness and disgust in subjects with right sided anterior amygdala damage(Anderson and Phelps 2000). This was interpreted as the right amygdala mediating the detection of affective states linked to withdrawal or avoidance. However, against this interpretation, it could be argued that angry expressions are as likely to evoke withdrawal as approach behaviours. Similarly the expressions of surprise from the Ekman series includes examples which most people would rate as portraying 'unpleasant' surprise (which would evoke withdrawal) rather than pleasant surprise (approach). Finally, in both the Anderson study and our study there was also no evidence of any deficits in the approach related emotions among those with left amygdala lesions.

Models which link deficits in the recognition of groups of emotional categories with dysfunction in specific behavioural dispositions or communication styles are still tentative. In an effort to determine the significance of these subtle deficits we will later link emotion recognition impairments with other social cognitive skill deficits, including the recognition of more complex emotional expressions, reasoning about the emotional states of others and measures of empathy.

4.6.5 Limitations.

Adolphs and colleagues recently demonstrated that the inability to recognize fear from facial expressions shown by patient SM with bilateral amygdala damage is explained by her highly abnormal pattern of scanning the face, specifically a tendency not to fixate on the highly informative eye region(Adolphs, Gosselin et al. 2005). When instructed to fixate on the eye-region her recognition of fear was significantly improved. Thus in future work it would be important to examine the eye tracking of patients with unilateral amygdala damage to see if the right amygdala subjects show a similar abnormal scanning pattern. Secondly, although a large study, with a clinical control group, the sample size is sufficient only to detect large effect sizes since performance variation between individuals within the groups was wide. This may in part explain the failure to detect a significant difference between the amygdala and clinical control groups, although the pattern of results was as expected. It could also be argued that the methods employed may not have been sensitive enough to detect very subtle impairments in the processing of facial expressions of happiness, surprise and anger, which could be overcome by manoeuvers such as presenting morphed blends of the emotions(Adolphs and Tranel 2004). We did not exclude the possibility that the amygdala damage subjects had problems in the understanding of the basic emotional terms through, for example, asking for definitions or situations in which the emotions would be experienced. However, Anderson and others have found that subjects with unilateral amygdala damage were able to generate sentences which typified the six basic emotional terms(Anderson and Phelps 2000).

4.5.6 Links with emotional memory study.

The results are of relevance to our earlier finding that emotional enhancement of memory is disrupted by early but not late damage to the amygdala. The comparable

deficits in emotion recognition found in the early and late amygdala groups in emotion recognition might suggest that the emotionally arousing material is perceived in a similar manner by both groups. Thus failure to detect the material as frightening (eg the slide of the car knocking down the child) or sad (eg the slide of the mother looking distraught) is unlikely to underlie the differential recall. Of course the stimuli used in the emotional memory story are much more complex than the Ekman and Friesan faces.

4.6 Conclusion.

Our study however has perhaps two central points. Firstly, deficits in emotional facial expression recognition are subtle. Whatever the role of the amygdala, it is likely to only form part of a distributed system. Equally, the right amygdala does appear to have a particularly important role in the 'on-line' recognition of fear and sadness

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Chapter 5 Recognition of facial expressions of more complex emotions

5.1 Summary

Humans can detect facial expressions of both basic emotions and expressions reflecting more complex states of mind. The latter includes emotional expressions that regulate social interactions (social expressions such as looking 'hostile' or 'friendly') and expressions that reflect the inner thought state of others (cognitive expressions -such as looking 'thoughtful' or 'daydreaming'). Previous work suggests that the amygdala is important in the recognition of social, but not cognitive, expressions (Adolphs, Baron-Cohen et al. 2002). To explore the neural substrate of this skill we examined performance on a test of recognition of such complex expressions in patients with lesions involving or sparing the amygdala and healthy controls. The effect of the stage of development in which amygdala damage was acquired was explored by comparing subjects with lesions thought to arise early in development with subjects whose damage occurred in adulthood. We found that damage to either amygdala was associated with impairment in the recognition of both complex expressions, despite an intact ability to extract information relating to the invarient physical attribute of gender. Contrary to our expectations, the impairments were most marked in expressions which reflected the 'cognitive state' of an individual, rather than in the detection of 'social' expressions. There was no evidence to support our hypothesis that early amygdala damage would be associated with more severe deficits in this task. These results are congruent with a role for the amygdala in on line processing of a wide range of complex emotional expressions.

Some of the findings of this study have been published in the *Journal of Cognitive Neuroscience* (paper included at end of thesis).

5.2 Introduction.

As can be gleaned from previous chapters, there has been considerable progress in uncovering the neural substrate of the detection of so-called basic emotional expressions. A key question is to what degree the same neural circuitry is employed for the recognition of more complex emotional expressions.

There is no universally accepted typology of facial expressions, but one widely used division separates the six basic emotions (fear, sadness, disgust, anger, surprise and happiness) from more complex expressions (Ekman, Sorenson et al. 1969; Adolphs 2001). The complex expressions can be further divided into 'social expressions', which intimately regulate social behaviors, and 'cognitive expressions' which reflect the inner thought state of an individual (Adolphs, Baron-Cohen et al. 2002). The social expressions can only be understood in a social context and typically have a clear valence, either positive (e.g. 'friendly') or negative (e.g. 'hostile' or 'contemptuous'). Cognitive expressions, by contrast, can be considered to provide a display of the inner thought state of an individual, and do not have such a clear valence (examples are looking 'pensive', 'thoughtful', or 'contemplative'). Support for this division comes partly from studies of patients with amygdala lesions, who, it is claimed, are impaired in the recognition of social, but not cognitive expressions (Adolphs, Baron-Cohen et al. 2002). The further sub-division of social expressions on the basis of valence receives some validation from studies suggesting that the right hemisphere processes stimuli with a negative valence, and the left hemisphere

processes stimuli with a positive valence (Davidson 1992; Davidson 1993; Mandal, Borod et al. 1999).

Lesion studies have again proved valuable in delineating the neural substrate of the recognition of complex emotional expressions. For example, Adolphs and colleagues demonstrated impairments in matching social, but not cognitive, complex emotional expression to correct descriptors in patients with unilateral amygdala damage (Adolphs, Baron-Cohen et al. 2002). The deficits were particularly marked in two patients with bilateral damage, and surpassed impairments in the recognition of basic emotions. Adolphs et al., also reported on three patients with complete bilateral damage to the amygdala who consistently rated faces as trustworthy, unlike healthy controls and subjects with unilateral amygdala damage who rated the same faces as being untrustworthy (Adolphs, Tranel et al. 1998). This deficit was not found when the patients were asked to make similar judgments based on verbal material. The authors suggested that the amygdala thus acts as a trigger, allowing visual stimuli, particularly faces, to access stored social knowledge. The implication of the amygdala in the recognition of a range of complex mental states is also supported by fMRI studies which have demonstrated amygdala activation in healthy subjects during presentation of pictures of faces depicting complex social mental states or attributes (eg trustworthiness) (Baron-Cohen, Ring et al. 1999; Winston, Strange et al. 2002; Winston, O'Doherty et al. 2003).

We ask again whether the developmental stage of amygdala damage has any impact on the recognition of complex emotional expressions. To summarize the central questions: firstly, does early amygdala damage cause greater disruption to the

recognition of complex expressions? What are the effects of late amygdala damage? If the amygdala is only necessary for the acquisition of skills pertinent to the recognition of complex expressions, and not its 'on-line' performance, then no impairment would be expected in this group. If however the amygdala mediates the 'on-line' visual recognition of complex expressions, then the loss of the amygdala in adulthood would be associated with impairments.

Current evidence favours an 'on-line' role, as two of the three bilateral amygdala damage patients studies by Adolphs and colleagues acquired their damage in adulthood. However, patient SM, who had Urbach-Wiethe disorder which is likely to have caused amygdala damage in her childhood, was the most severely impaired. This is consistent with compounded effects of early damage to a structure necessary both for the acquisition and performance of a skill.

The question also arises as to whether damage to left or right amygdala has similar effects. The emphasis many researchers have placed on differential hemispheric specialization in the processing of emotions has already been discussed, but has not been considered in the recognition of complex emotional expressions. Several positions have emerged: firstly, that the right hemisphere is responsible for the processing of all affective signals regardless of valence (Bowers, Bauer et al. 1993; Kucharska-Pietura, Phillips et al. 2003) ; secondly that hemispheric differences align with intrinsic properties of the emotional stimuli: thus the right hemisphere may be specialized for the processing of stimuli with a positive and the left hemisphere for stimuli with a negative valence(Silberman and Weingartner 1986; Borod, Cicero et al. 1998; Weniger and Irle 2002). These asymmetries are sometimes linked to the

motivational properties of stimuli: thus one study has demonstrated that subjects with right sided damage to the anterior temporal lobe were impaired in the detection of facial expressions associated with withdrawal behaviours (Anderson, Spencer et al. 2000). A similar interaction of valence with laterality may also be found in the detection of more complex social expressions (which typically have either a positive of negative valence), but might not be expected in the more affectively neutral cognitive expressions.

To assess the recognition of complex expressions we used was the revised version of the 'Reading the Mind in the Eyes task' (abbreviated to the 'Eyes Task'). (Baron-Cohen, Jolliffe et al. 1997; Baron-Cohen, Wheelwright et al. 2001). This requires subjects to detect the mental states of another on the basis of the appearance of a photograph of the eye region. It includes items which depict complex cognitive expressions reflecting the internal cognitive state of individuals (such as pensive or daydreaming) and social expressions, both positive and negative in valence.

5.3 Hypotheses

We hypothesised that:-

1) Lesions of the amygdala would be associated with impairment in the recognition of complex emotional expressions, but in the recognition of invariant physical attributes (gender) compared with healthy and clinical controls,.
2) Early damage to the amygdala would be associated with more profound impairments than late amygdala damage.
3) Deficits would be found for social, but not cognitive, emotional expressions.

4) We predicted that right amygdala damage would impair recognition of social expressions with a positive valence and left amygdala damage impair recognition of social expressions with a negative valence.

5.4 Methods

5.4.1 Participants

1) Early amygdala damage group have been described in detail in earlier chapters. In this study there were six subjects with right and ten with left amygdala damage.

2) Eleven subjects with late amygdala damage. As only two had left sided damage it was not possible to look for laterality effects within this group, and the subjects with right and left sided damage were thus combined.

3) Clinical controls. There were 12 subjects with focal lesions sparing the amygdala (5 with right sided and 7 with left sided damage).

4) Healthy controls. 81 subjects with no history of neurological or psychiatric disorders were recruited, from a database held at the Institute of Psychiatry and through personal contacts. There were a large number of healthy control subjects in this study which was carried out in part with Dr E Lawrence, who tested 31 of the healthy control subjects.

5.4.2 Tasks

IQ was estimated from subtests of the WAIS-III in the clinical groups (vocabulary and similarities for verbal IQ and block design and object assembly for performance

IQ). All healthy subjects completed the National Adult Reading Test (NART) to estimate intelligence (Nelson 1982). All clinical subjects also completed the Benton Facial Recognition test (Benton, Sivan et al. 1983).

In the 'Reading the Mind in the Eyes' task (revised version) –or "Eyes task"- subjects are presented with pictures of the eye-region of actors. The pictures are flanked by four terms (the correct term and three foils) and the subjects are asked to choose which term best describes what the actor is thinking or feeling(Baron-Cohen, Wheelwright et al. 2001). The terms do not include any basic emotional descriptors (happy, sad, angry, frightened, disgusted or surprised). To ensure subjects understand the terms, a glossary of definitions is provided and subjects encouraged to ask about the meaning of any unfamiliar words. As a non-emotional control face-processing task, subjects are asked to judge the gender of the actor

In this study, four independent assessors divided the stimuli into those which depicted cognitive expressions (e.g. 'pensive' 'daydreaming' 'contemplative') or social expressions. Social expressions include those with a positive valence (e.g. flirtatious, playful, friendly) and those with a negative valence (e.g. hostile, suspicious, defiant, accusing). Only items on which there was complete agreement on the categorization were included in further analyses; thus the totals for the social (11 stimuli) and cognitive stimuli (16 stimuli) do not equal the total for the entire stimulus set (36 stimuli). One of the stimuli is shown in Figure 5.1 and the test can be downloaded for research purposes at www.autismresearchcentre.com.

Figure 5.1: an example of a stimulus from the 'Eyes' task. In this picture the correct answer is 'friendly', and thus is an example of a complex social expression.

A score of 1 point was given for a correct answer, and 0 for an incorrect answer. Scores were converted to percentages to allow comparisons in the performance across the cognitive and social expressions.

5.5 Results

5.5.1 Demographic characteristics (Table 5.1)

Subjects differed in verbal IQ ($F(3,111)=26$, $p<0.001$), with all clinical groups scoring lower than the healthy controls ($p<0.01$). As verbal IQ was different between groups and correlated with overall scores ($r=0.43$, $p<0.001$), it was entered as a covariate.

The groups did not differ significantly in age at testing, nor did the clinical groups in duration of seizures. There was a significant difference in the proportions of subjects with right sided damage between the clinical groups ($\chi^2=6.4$, $p=0.04$), but not in

gender (χ^2=0.94, p=0.82). The impact of the unequal proportions of subjects with rigth sided damage in each group is explored further in the discussion. The small number of subjects with left sided damage in the late amygdala group essentially prohibited an exploration of any interaction of stage with side of damage.

Table 5.1 Demographic characteristics

	Side R: L	Gender M:F	Age	Verbal IQ	Benton facial recognition task	Duration of seizures: mean (SD) , y
Early amygdala	6:9	6:8	34 (11)	97 (15)	42 (3)	20 (13)
Late amygdala	9:2	5:7	33(12)	97 (15)	44 (4)	15(11)
Clinical controls	4:8	4:8	30 (7)	89 (12)	43 (2)	14 (8)
Healthy controls	-	31:28	35 (11)	112 (13)	-	-

5.5.2 Experimental task

There was no difference between groups in performance in the control task of gender identification, with all groups performing near ceiling (F(3,92)=12., p=0.31).

Table 5.2 Scores (as a percentage) in the control task of gender recognition.

	N	Mean	SD
Early amygdala	15	95	4
Late amygdala	11	95	5
Clinical controls	12	94	6
Healthy controls	83	96	4

5.5.3 The effects of amygdala damage

All subjects with damage to amygdala (regardless of side or stage) were compared with the healthy and clinical controls in overall performance – see Table 5.3. The significant group difference ($F(2,118)=17.1$, $p<0.001$) was explored by post hoc pairwise comparison tests with Bonferroni correction which showed a significant impairment in the amygdala group relative to healthy controls (adjusted $p<0.001$) and a near significant impairment relative to the clinical controls (adjusted $p=0.06$). The group difference held on entering verbal IQ as a covariate ($F(2,111)=8.1$, $p=0.001$) and the difference between the amygdala group and both control groups reached significance (at adjusted $p<0.01$).

Table 5.3 Scores (as a percentage) in recognition of complex expressions.

	N	Mean	SD
Amygdala damage	26	61	16
Clinical controls	12	71	10
Healthy controls	83	76	10

To explore the effect of category of expressions, a repeated measures ANOVA with category of expressions as within subjects factor, and group as the between subjects factor was conducted. Assumptions of sphericity were not met and thus a conservative Greenhouse-Geisser adjustment was made. If, as we predicted amygdala damage specifically impairs the recognition of social but not complex expressions, then a significant interaction of group and expressions would be found. This was not the case, ($F(2,118)=1.2$ $p=0.3$) and if anything, the trend was in the opposite direction.

The main effect for group ($F(2,118)=13.6$ $p<0.001$) held, and the pattern of results was not altered by including verbal IQ as a covariate.

Table 5.4 Scores (as a percentage) in recognition of complex cognitive and social expressions.

		Cognitive		Social	
	N	Mean	SD	Mean	SD
Amygdala	26	57	18	65	26
Clinical controls	12	69	14	71	19
Healthy controls	83	76	14	77	15

5.5.4 The effects of early versus late amygdala damage

To examine developmental effects, we compared the early, late amygdala and control groups. Scores for the recognition of all complex expressions differed significantly, $F(3,117)=12.1$, $p<0.001$. Pairwise contrasts with Bonferroni correction showed the early amygdala scores to be lower than the healthy controls (adjusted $p<0.001$) and the late amygdala scores to be lower than both the clinical controls (adjusted $p=0.05$) and the healthy controls (adjusted $p<0.001$). The group difference remained after entering verbal IQ as a covariate ($F(3,110)=6.1$, $p=0.001$) and the differences between the late amygdala damage and clinical (adjusted $p=0.007$) and healthy controls (adjusted $p=0.001$) persisted, although the early amygdala impairment did not hold relative to healthy controls($p=0.18$). There were no significant differences between the early and late amygdala damage groups.

Table 5.5 Scores (as a percentage) in recognition of complex expressions for early and late amygdala damage groups.

	N	Mean	SD
Early amygdala	15	64	18
Late amygdala	11	57	15
Clinical controls	12	71	10
Healthy controls	83	76	10

Category of emotion was explored as before using repeated measures ANOVA. There was a significant group difference ($F(3,117)=93$. $p<0.001$) with the early and late amygdala group impaired relative to healthy controls (adjusted $p<0.01$). The difference between the late amygdala damage and clinical controls was no longer significant, possibly due to the analyses including only a subset of the total stimuli, resulting in a loss of power. Again, there was no significant interaction of category of expressions and group ($F(3,117)=1.2$, $p=0.3$) suggesting that early and late amygdala damage had similar effects on the recognition of both expression categories. Indeed examining the raw data, the deficits in the recognition of cognitive expressions suggest greatest impairment in the recognition of cognitive expressions in the late amygdala group.

Table 5.6 Scores (as a percentage) in recognition of complex social and cognitive expressions for early and late amygdala damage groups.

		Cognitive		Social	
	N	Mean	SD	Mean	SD
Early amygdala	15	61	18	65	28
Late amygdala	11	52	17	64	25
Clinical controls	12	69	14	71	19
Healthy controls	83	76	14	77	15

5.5.5 Laterality effects

In exploring laterality effects, due to the small numbers of subjects with left sided damage in the late amygdala group, subjects from the early and late groups were combined for these analyses. Similarly the subjects in the clinical group were combined as the there were only two with left sided damage, whose scores lay near the median score of the nine subjects with right sided damage. There was a significant group difference in overall scores ($F(3,117)=11.4$, $p<0.001$) with both the right and left amygdala damage group scoring less than healthy controls ($P<0.001$), but no other group differences.

Table 5.7 Scores for right and left amygdala damage groups (combining early and late damage participants)

	N	Total		Cognitive		Social	
		Mean	SD	Mean	SD	Mean	SD
R amygdala	15	60	19	54	19	67	30
L amygdala	11	62	14	61	16	63	21
Clinical controls	12	71	10	69	14	71	19
Healthy controls	83	76	10	76	14	77	15

We predicted an interaction of valence of social emotion and the side of amygdala damage, in line with the theory that right sided amygdala damage would more seriously impair the recognition of social expression with a negative valence and left sided amygdala damage impair recognition of positive social expressions. This was tested with a repeated-measures ANOVA with positive and negative social emotions as within subjects factor. There was no significant interaction, $F(3,117)=0.83$, $p=0.48$, and thus this hypothesis was rejected.

5.6 Discussion

5.6.1 Summary

1) Lesions of the amygdala are associated with significant impairment in the recognition of complex expressions despite an intact ability to detect a physical property (gender) from the same stimuli.
2) Contrary to our prediction, subjects with early amygdala damage were not more impaired than those with late amygdala damage. While both the early and late group were impaired relative to healthy controls, only the late amygdala damage group were impaired relative to the clinical controls.
3) We found no evidence to support our hypothesis that amygdala damage would result in greater deficits in the recognition of social rather than cognitive expressions.
4) No robust laterality effects emerged. Right or left amygdala damage was associated with impairment relative to healthy controls.

5.6.2 The amygdala and recognition of complex expressions

The study is a partial replication of Adolphs' examination of the effects of anterior temporal lobectomy on the recognition of complex facial emotional expressions which in part used the same basic paradigm (Adolphs, Baron-Cohen et al. 2002). The finding of a role for the amygdala in the detection of a broad range of complex emotional expressions may seem to run counter to the findings of specific deficits in the recognition of fear and sadness among the basic emotions which we reported earlier. There are several possible explanations for this apparent discrepancy. Firstly many other groups report deficits in the processing of all the basic emotions, particularly in patients with bilateral amygdala damage. This was most convincingly

demonstrated in a case series of ten subjects with Urbach-Wiethe disease, all of whom showed a degree of bilateral amygdala degeneration. Abnormal perceptual judgments were made to all the basic emotions, both of positive and negative in valence, in facial stimuli(Siebert, Markowitsch et al. 2003). The functional imaging literature also lends only inconsistent support to the concept of a highly modular role for affective processing by the amygdala. Although there are some reports of specific amygdala activation to facial expressions of fear rather than the other basic emotions, many studies do not report such specificity (Zald 2003). There are also increasing reports of amygdala activation to positively valenced stimuli in multiple modalities(Garavan, Pendergrass et al. 2001; Hamann, Ely et al. 2002; Yang, Menon et al. 2002). In a study which independently manipulated a range of stimulus attributes, the amygdala was found to be consistently activated bilaterally in healthy controls when presented with four of the basic emotions, including happy faces(Winston, O'Doherty et al. 2003). Thus some findings from lesion and functional imaging studies converge to support a general role for the amygdala in processing a wide range of facial expressions. This line of argument posits that the amygdala may be involved in the processing of all the basic emotions and thus by extension perhaps more complex facial expressions.

However, there are several problems with this general affective processor model ofamygdala function. Firstly, our earlier study is by no means the only lesion study to argue for a more specific role, limited to certain classes of emotional stimuli. More importantly we found deficits in the recognition of complex cognitive stimuli, which are not generally affectively charged, to equal (and perhaps surpass) the impairment in recognition of affectively charged social expressions. Thus, our findings may

reflect some other properties of the putatively 'cognitive' stimuli. As noted by Baron-Cohen, many of the cognitive expressions share the property of averted eye-gaze of the actor, present in 12 of the 16 cognitive stimuli in the 'Eyes' task (Baron-Cohen, Whelwright et al. 1997). By comparison, in all of the social stimuli, the actor is looking directly toward the viewer. The difference between the proportions of the social and cognitive stimuli with direct gaze is significant (χ^2=14.8, p<0.001). The amygdala has an important role in monitoring the direction of eye gaze. Patients with bilateral amygdala damage experience difficulty identifying gaze direction (Young, Aggleton et al. 1995). In healthy subjects, functional imaging suggests that the amygdala is recruited when eye gaze direction is being actively monitored (Hooker, Paller et al. 2003), not just in conditions of direct or averted eye gaze (Kawashima, Sugiura et al. 1999). It is feasible that categorizing conditions where there is direct eye gaze (most social expressions) may prove less challenging than conditions with averted eye gaze (cognitive expressions) for subjects with an impaired gaze monitoring system due to amygdala damage. Alternatively, an accurate apprehension of eye gaze direction may be more pertinent to the detection of cognitive expressions.

The current study is only a partial replication of the previous report of deficits in the decoding of complex expressions among patients with damage to either amygdala(Adolphs, Baron-Cohen et al. 2002). That study further found evidence of a selective deficit among patients with amygdala damage in the recognition of social, but not cognitive, expressions. Our results showed no significant difference between the categories of expression, and indeed suggested greater impairment in the recognition of cognitive expressions. It is unlikely that the differences are due to factors in the design, as both studies used the same stimuli. Factors relating to the participants are more likely to account for the differences. For example, in the

Adolphs et al. study the patients had variable amounts of amygdala damage, unlike the uniform total excision in the patients we studied. In line with Adolphs study we also did not find any robust effects of side of damage. This might in part reflect the nature of the task which relied on decoding the eye-region of the face alone- an activity which engages both amygdalae.

5.6.3 Limitations of the task.

The 'Eyes task' was originally described as an advanced test of theory of mind on the grounds that it involves the attribution of a relevant mental state (e.g. daydreaming). Clearly it does not include the second stage of inferring the content of that mental state (eg daydreaming *about* a impending holiday)(Baron-Cohen, Wheelwright et al. 2001). However, some reserve the term 'theory of mind' for tasks which incorporate both stages. In this paper we therefore use different terminology, dividing the stimuli into cognitive and social expressions. The distinction we employ has proved useful in other neuropsychological studies although we acknowledge that there are many other ways of classifying the stimuli (Adolphs, Baron-Cohen et al. 2002)

The 'Eyes task' has been analyzed as requiring subjects to have a lexicon which includes cognitive (thought-state), social emotional or mental state terms and to know the semantics of these terms. The task involves mapping these terms to the stimuli presented (the eye region of the human face)(Baron-Cohen, Wheelwright et al. 2001). The mean score on the 'Eyes Task' for healthy controls in our study was similar to the normative scores given in the original report of the task(Baron-Cohen, Wheelwright et al. 2001). The test has proved to have concurrent validity in that it correlates well with measures of personality traits of empathic understanding (Lawrence, Shaw et al.

2004) It is also sensitive to deficits in adults with Asperger's syndrome who have core deficits in aspects of social cognition (Baron-Cohen, Wheelwright et al. 1999). It also benefits from a knowledge of the neural substrate supporting its performance in healthy subjects derived from both functional imaging and ERP studies (Baron-Cohen, Ring et al. 1999; Sabbagh, Moulson et al. 2004). However, the control condition of gender assignment differs in its level of difficulty as there are only two choices, and these choices are fixed throughout (male versus female). This may have resulted in a partial ceiling effect obscuring group differences. The stimuli were of the human eye region only and static in nature, features which might be criticized for lacking ecological validity. However, previous studies have shown that the detection of complex mental states from the eye region does not differ greatly when the entire face region is used (Baron-Cohen et al .1997).

Although this is one of the largest studies with unilateral focal lesions of the amygdala and prefrontal cortex in social perception there is still a risk of type 1 errors when the performance of subgroups are considered. There is also some variability in the extent of exact damage within each group, particularly among the patients with focal lesions of the temporal lobe.

The amygdala plays an important role in interpreting eye gaze, and deficits in recognition of facial expressions of basic emotions such as fear can be ameliorated when patients are guided in making eye contact within the face (Adolphs and Tranel 2003). Thus the patients with amygdala lesions in this study may simply not have been performing the task normally, perhaps scanning the stimuli in a highly aberrant manner. As we did not track the eye movements of patients during the task we cannot

exclude this possibility. However, two findings suggest that the patients were processing the stimuli to some degree. Firstly, the patients with amygdala damage were intact in the control condition and were thus able to extract information relating to a non-emotional, physical property. Secondly, the patients were not significantly impaired in the recognition of social expressions, relative to those with focal non-amygdala damage. However, future studies with patients who have lesions of the amygdala would benefit from detailed examination of how they scan the stimuli.

5.7 Conclusions.

Damage to either amygdala impairs the recognition of complex expressions, depicting the social intent and cognitive states of others. The deficits are present in those with both early and late amygdala damage, compatible with an 'on-line' role for the amygdala in decoding complex facial expressions from information contained in the eye region. This is congruent with functional imaging studies implicating the amygdala in processing of aspects of eye gaze, particularly those related to affective dimensions. We found little evidence for lateralisation of function in this task. This is somewhat at odds with our earlier finding of right amygdala processing of fear and sad facial expressions, but may reflect the use of stimuli confined to eye region of the face.

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Chapter 6: Theory of mind reasoning and the amygdala.

6.1 Summary

There is a burgeoning interest in the neural basis of the ability to attribute mental states to others; a capacity referred to as 'theory of mind' (ToM). We examined the effects of lesions of the amygdala which arise at different stages of development on this key aspect of social cognition. Tests of ToM, executive and general neuropsychological function were given to subjects with lesions of the amygdala arising congenitally or in early childhood ('early damage', n=15), subjects who acquired damage to the amygdala in adulthood ('late damage' n=11) and matched clinical (n=14) and healthy comparison groups (n=57). We found that subjects with early damage to the amygdala were impaired relative to all other groups on more advanced tests of ToM reasoning- such as detecting tactless or ironic comments or interpreting non-literal utterances. These deficits held for subjects with either left or right early amygdala damage and encompassed the understanding of both the beliefs and emotional states of others. By contrast, subjects who acquired damage to the amygdala in adulthood (usually as part of an anterior temporal lobectomy) were not impaired in ToM reasoning relative to both clinical and healthy controls, supporting the position that the amygdala is not part of neural circuitry mediating the 'on-line' performance of ToM reasoning. In line with theories which claim that ToM is an independent faculty of cognition, we found the pattern of results held after co-varying for measures of executive function, memory and general intellectual functioning. We discuss the results in the light of recent theories which link early developmental insults to the amygdala with the ToM impairments which are thought to be a core neurocognitive deficit found in disorders such as autism. We conclude that the

amygdala may play an important role in the neural systems supporting the normal development of ToM reasoning.

Some of the findings from this study have been published in the journal *Brain* (paper included at the end of the thesis).

6.2 Introduction

The term 'theory of mind' (ToM) has been applied to the capacity to attribute mental states to others in order to understand and predict their behaviour (Premack and Woodruff 1978). Several models of the neural circuitry mediating this key aspect of social cognition have already been developed on the basis of functional neuroimaging, human lesions and primate studies. The amygdala has been included in many models of ToM reasoning as part of a distributed network which includes other regions of the temporal lobe (particularly the polar cortex and superior temporal gyrus) and frontal lobes (the orbitofrontal cortex and anterior cingulate cortex) (Brothers 1989; Baron-Cohen, Ring et al. 1999; Tager-Flusberg and Sullivan 2000; Abu-Akel 2003; Adolphs 2003; Frith and Frith 2003; Stone, Baron-Cohen et al. 2003).

Several positions have emerged concerning the exact role of the amygdala in the mediation of reasoning about the mental states of others. Firstly, some theorists place the amygdala at the very core of the neural circuitry which supports ToM reasoning and argue it is necessary both for the development of the ability to reason about others and is a component of the 'on-line' circuitry recruited during performance of ToM tasks (Brothers 1989; Baron-Cohen, O'Riordan et al. 1999; Stone, Baron-Cohen et al. 2003). In support of the necessity of the amygdala in the development of ToM

abilities, there are case reports of subjects with lesions of either one or both amygdalae which arise early in development who show impairments on a range of tasks requiring ToM reasoning (Fine, Lumsden et al. 2001; Heberlein and Adolphs 2004). People who have autism have consistently been found to exhibit deficits in ToM reasoning, which are thought to underpin many of the anomalies in social behaviour typical of autism (Baron-Cohen, Leslie et al. 1985). This has been explicitly linked to structural, and by implication functional, developmental abnormalities of the amygdala, with reports of both macroscopic and microscopic abnormalities (Howard, Cowell et al. 2000; Amaral, Bauman et al. 2003; Baron-Cohen 2004). Similarly cortical tubers which develop within the temporal lobes during fetal life have been associated with autistic comorbidity among people who have tuberose sclerosis (Bolton and Griffiths 1997).

Evidence for the necessity of the amygdala in the adult 'on-line' performance of ToM tasks comes from human lesion and functional neuroimaging studies. Stone et al. describe two subjects who acquired damage to the amygdalae in adult life who are impaired in the attribution of mental states to others on the basis of the appearance of the eye region and also in the ability to detect when a character in a story had unintentionally hurt the feelings of another (Stone, Baron-Cohen et al. 2003). Larger group studies have demonstrated acquired deficits in ToM tasks among adult subjects with both left and right hemisphere cerebrovascular insults, which may have compromised the blood supply to the amygdala from the deep perforating branches of the middle cerebral artery (Happe, Brownell et al. 1999; Channon and Crawford 2000). The findings of the lesion studies are corroborated to some extent by findings from functional MRI. In healthy subjects the amygdala is activated when judgements

are made about the mental states of others on the basis of their appearance (Baron-Cohen, Ring et al. 1999; Winston, Strange et al. 2002) and when mental states are attributed to the movements of abstract shapes, as in the Heider and Simmel paradigm (Castelli, Happe et al. 2000; Castelli, Frith et al. 2002).

A second position holds that while the amygdala may support the development of ToM skills, it is not a critical component of the circuitry which supports the 'on-line' performance of ToM reasoning in adulthood. In this vein, Frith and Frith have highlighted in their synthesis of functional MRI studies that although some studies have demonstrated amygdala activation during the performance of ToM reasoning tasks, such studies are the exception rather than the rule (Frith and Frith 2003). They and other authorities (Tager-Flusberg, Boshart et al. 1998; Tager-Flusberg and Sullivan 2000) have argued that the amygdala is more likely to support the development (and on-line performance) of basic social perceptual abilities which are taken to be the precursors or 'protoforms' of ToM knowledge. We have given evidence for the deleterious effects of both early and late amygdala lesions on emotional perception and mentioned the functional imaging evidence demonstrating activation of the amygdala during the 'on-line' adult perception of basic and complex emotional states (for a review of fMRI studies see (Zald 2003) and for a review of other lesion studies see (Adolphs 2003) and the previous chapters). As skills such as the perception of the emotional states of others develop into the ability to reason about these mental states, there is a concomitant shift from a reliance on phylogenetically ancient structures such as the amygdala to frontal cortical regions. It is argued that without these social perceptual skills the attainment of ToM skills is at the very least delayed and rendered error prone in contrast to the qualitatively effortless and

accurate ToM attributions found in healthy subjects. Thus, in these models the amygdala is not thought to be necessary for the on-line *execution* of ToM reasoning; however its role in supporting the precursors of ToM reasoning may make its integrity a necessary but not sufficient condition for the *development* of normal ToM abilities.

We can use our subjects to compare these two theoretical positions by examining ToM reasoning among subjects who acquire lesions to the amygdala early in development (either congenitally or in early childhood) with those who acquire damage in adulthood to a normally developed amygdala. Both positions would predict that subjects with early damage would be impaired in ToM reasoning. If the amygdala additionally supports adult 'on-line' ToM reasoning, then we would predict similar ToM impairments in subjects with damage acquired in adult life. If however the amygdala has a purely developmental role and is not involved in the adult 'on-line' execution of ToM reasoning then we would expect relatively intact ToM performance among those with amygdala damage acquired in adulthood.

A third theoretical position argues that the amygdala is only part of the substrate of reasoning about the mental states of others in so far as it supports domain-general cognitive functions (Frye 2000). Some have argued that there is no need to invoke a domain specific ToM module and instead emphasised the frequent presence of executive dysfunction among many subjects with ToM impairments (Channon and Crawford 2000). However there are already several case reports, including a subject with an amygdala lesion, suggesting that ToM impairment can occur even in the presence of intact executive function- a dissociation in favour of a modular ToM mechanism (Bach, Happe et al. 2000; Fine, Lumsden et al. 2001; Rowe, Bullock et al.

2001). Further detailed examination of subjects with focal lesions of the amygdala may shed light on the issue: prominent executive dysfunction, general intellectual and language impairment would not be expected in this group, and thus any deficits in 'theory of mind' reasoning would not be readily reduced to impairments in other cognitive systems.

Other emergent themes in research on the amygdala include the possible impact of laterality on amygdala function, in domains such as the perception of, and memory for, emotionally salient stimuli (Zald 2003). In 'theory of mind', several groups have reported laterality differences in ToM reasoning with prominent deficits among subjects with right, but not left, hemisphere damage (Happe, Brownell et al. 1999). Other human lesion studies and one functional imaging study report exactly the opposite pattern (Channon and Crawford 2000).

There has been increasing interest in exploring different forms of ToM reasoning. It has been proposed ToM reasoning which pertains to affective or emotional states of others (part of the so-called 'hot cognitive processes') might be dissociable from ToM reasoning about epistemic or belief states (so-called 'cold cognition'). This theoretical division is a development of the model of social cognition initially proposed by Brothers(Brothers and Ring 1992; Stone, Baron-Cohen et al. 2003). Brothers and others have argued that 'hot' social cognitive processing is largely supported by the amygdala, and 'cold' social cognitive processing by orbitofrontal cortex. More recently, Stone and colleagues have speculated that these different types of mental states may have lateralised processing at the level of the amygdala (Stone, Baron-Cohen et al. 2003). In their faux pas task subject DR who had predominately

right sided amygdala damage was most impaired in affective state attributions- i.e. realising that a person would feel hurt or insulted when confronted with a tactless comment. In contrast, subject SE who had more prominent left sided amygdala damage made more errors in appreciating that the tactless comment was made unintentionally- thus showing impairment in epistemic or belief attribution. This is similar to the subject described by Fine et al who had more selective left sided amygdala damage and was impaired on a range of ToM tasks which assessed mainly epistemic (belief) mental state attributions(Fine, Lumsden et al. 2001). We aimed to further explore this possible dissociation of the ability to reason about the epistemic and affective mental states of others. To some extent this division is analogous to the split between social and cognitive complex expressions we discussed earlier.

We thus developed a novel task in which participants are given vignettes which concerned two protagonists A and B. The scenarios centred on social situations, typically on themes of social exclusion or threat. In the vignette, A holds a true first order belief and B holds a false second order belief. Each belief is associated with an emotional state- in each scenario one of the emotional states has a positive valence and the other a negative valence. Participants are asked questions designed to assess their understanding of the two conflicting beliefs and conflicting emotional states. Control questions testing memory for the story and inference making are included.

Previous research into the neural basis of the development of ToM skills of previous findings is limited by its reliance on case studies, in which damage to the amygdala rises from a range of aetiologies and is typically accompanied by extensive extra-amygdala damage. We attempted to overcome such limitations by studying our large

group of subjects with relatively focal pathology of the amygdala stemming from lesion thought on clinical and neuroradiological grounds to be compatible with the presence of a dysembryoblastic neuroepithelial tumour- DNET or other low grade glioma. The details of these tumours and methods of estimating their developmental age have been discussed in earlier chapters.

In this study we employ both the approaches detailed earlier: for the primary analyses the early amygdala group is defined by the presence of a focal amygdala DNET (regardless of age of onset of seizures). In further exploratory analyses, the developmental age of the amygdala DNET is taken more conservatively to be the age at which it became clinically apparent, acting as an epileptogenic focus.

The age of onset of damage to the amygdala in those with operative damage to a previously normal amygdala is taken as before to be the age of excision of the amygdala. Comparisons are made with an appropriate clinical comparison group of patients with epilepsy arising from similar focal pathologies affecting the temporal or parietal lobe which completely spared the amygdala.

6.3 Hypotheses

We thus aimed to explore systematically the effects of early and late developmental damage to the amygdala on 'theory of mind.' We predicted that subjects with early amygdala lesions would be impaired on tests of ToM reasoning compared to both healthy and clinical comparison groups. In line with the earlier discussion, we also predicted that subjects who acquired damage to a normal amygdala in adult life would not show such impairments. We also examined the possibility that there may be an

interaction between the content of the ToM task and the side of amygdala which mediates its processing. Specifically on the basis of previous case reports we predicted that subjects with lesions of the left amygdala would show greater impairment on ToM tasks which involved epistemic attributions and subjects with right sided lesions would have greater impairment on affective state attributions.

6.4 Method

6.4.1 Participants

All clinical subjects were recruited from the regional neuroscience centre at King's College Hospital, London. Details of the subjects are given earlier. In brief, the early amygdala damage group (N=15) all had lesions which centred on the amygdala with minimal extension. The late amygdala damage group (N=11) had received surgical treatment for their epilepsy with an en bloc anterior temporal lobe resection. The clinical comparison group (N=14) had lesions which spared the amygdala (see table 1 for details of all lesions). Healthy controls (N=57) were recruited from a database of volunteers held locally with no history of neurological or psychiatric disorders.

6.4.2.Tasks

Clinical groups completed the vocabulary, digit span, comprehension and similarities subscales for verbal IQ, and the block design and object assembly subscales for performance IQ [Weschler D 1997a]. An estimate of IQ was obtained from the National Adult Reading test for the neurologically intact control subjects (Nelson 1982). Memory was assessed with the immediate and delayed logical memory test from the Weschler Memory Scale-third version[Weschler D 1997b]. Executive function was assessed using the Hayling and Brixton tests (Burgess and Shallice

1996; Burgess and Shallice 1996). The Hayling test provides a measure of the ability to inhibit a prepotent response as well as task initiation speed. The Brixton test is a rule detection and set shifting task.

False belief tasks.

The false belief tasks were adapted from vignettes designed by Baron-Cohen and colleagues with superficial changes made to make the content more suitable for adults (Baron-Cohen, Leslie et al. 1985; Baron-Cohen 1989). Subjects must predict the actions of character on the basis of the character's mistaken belief. Both first order ('Peter thinks that....) and second order tasks ('Susan thinks that Peter thinks....') incorporating control questions assessing comprehension and memory were included. Throughout all the testing, subjects were read the vignettes and also held their own copies to minimise memory load. Overall scores are expressed as percentages throughout to allow for comparison across tasks.

Happé's Strange Stories (Happe 1994)

In these vignettes characters typically say something they do not mean literally and the participant is required both to demonstrate comprehension of the statement and explain the possible motivations underlying it. Stories on themes of lying, double bluff, being tactful and persuasion were included (with minor superficial alterations). In line with Happé and collaborators we coded the responses firstly as correct or incorrect. They were then further coded as including a completely and explicitly correct mental state reference (scoring 2 points), a context appropriate mental state which only implicitly correctly answered the question or a response which contained no references to mental states but purely physical terms (both scoring 1 point) or an

incorrect responses (scoring 0 points). These scores were then expressed as percentages and used in the calculation of the cumulative scores across all tests.

Metaphor and irony (Happe 1993).

Several theorists argue that the understanding of metaphor can be achieved by grasping the intentions of the speaker- it thus requires a first order theory of mind. In contrast the comprehension of an ironic statement requires the ability to appreciate the thought of the speaker and also the speaker's attitude towards that thought- that is, have second order meta-representational abilities exemplified by a second order theory of mind. In each vignette the chief protagonist makes both a metaphorical and ironic comment and the participant is asked to interpret the intent of the protagonist. Responses were coded as correct or incorrect and converted to percentage scores.

Faux pas task (Stone, Baron-Cohen et al. 1998)

The faux pas task explicitly assesses various constituent components of theory of mind. In each of nine vignettes person A unintentionally says something which will hurt the feelings of person B. Participants were then asked if someone in the story had said something awkward (detection of the faux pas), to identify who made the faux pas and to explain why s/he should not have made the comment (the epistemic attribution- 'he didn't realise he....'). Subjects are also asked about the emotional response of person B (the affective attribution - 'He would feel hurt...'). Finally a question relating to story comprehension was given. One point was given for: correct detection of the faux pas and the person who had made it, a correct epistemic attribution and a correct affective attribution, giving a maximum score of 27, which was then converted to an overall percentage score. Nineteen of the healthy controls

completed a slightly different version in which more superficial changes had been made to the test. Analyses showed no differences between scores in this amended version and the original and thus results were combined. (Restricting the analyses to only the original set produced an identical pattern of results).

'Conflicting belief and emotion' task.

This is a novel task in which participants are given vignettes which concerned two protagonists A and B and centred on a social scenario, typically on themes of social exclusion or threat. In the vignette, A holds a true first order belief and B holds a false second order belief. Each belief is associated with an emotional state- in each scenario one of the emotional states has a positive valence and the other a negative valence (see appendix 2). Participants are asked in a random order, questions designed to assess their understanding of the two conflicting beliefs and conflicting emotional states. Control questions testing memory for the story and inference making are included.

An annotated example of one of the vignettes is given below.

Vignette

Peter and Linda are on their way to school. As they approach the entrance the school bully comes up to them and demands their dinner money. Linda is in the same class as the bully and immediately hands over her money. Peter, who's a year younger, refuses. The bully grabs him and says; 'I'll get you at lunch time.'

Later that morning the bully is particularly loud and badly behaved in class: no-one including Linda can get any work done. Eventually the teacher decides that he has no option but to send the boy home. He calls the boy's parents and they come and collect him. Linda decides that she'll run and tell her friend what's happened as soon as the lunch break bell rings.

In another class room, Peter is gazing out the window. He happens to see the bully being taken home by his parents.

An hour later the lunch bell rings. Linda immediately dashes out of the classroom intending to go immediately to her friend.

Mental state reasoning questions

[second order false belief] Why is Linda in such a hurry?

[second order emotion] How does Linda think her friend Peter has been feeling?

[first order emotion] How has Peter been feeling/are there any changes in how he's been feeling?

[first order belief] By the end of the story does Peter think the bully is going to beat him up at lunchtime or not?

Control questions

[memory] Who is older: Peter or Linda?

[inference] What does Peter's classroom overlook?

Scoring criteria for this test are as follows. For the first order true belief the response is a forced choice (true or false) response. Responses to the second order false belief: were coded using the same method as in the Happé strange stories with responses categorized as containing a full mental state, partial mental state, or physical state response(Happe 1994). A full mental state response contains a full, explicit reference to appropriate and correct epistemic states for both protagonists in the vignette. The classic form of the response is 'X thinks that Y thinks'. Any reasonable synonym for an epistemic/belief state is acceptable (believes wonders, suspects, guesses etc.). A partial mental state response contains a reference to the epistemic state of one of the

protagonists only. The answer is appropriate and correct but incomplete. A typical response would be 'He is worried about her', 'He thinks she has failed". If a partial mental state response is given, participants are not further prompted to expand on the answer as one of the main interests of the test is the quality of spontaneous mental state reasoning. A physical response is again appropriate and correct in the context of the vignette but contains no mental terms. Mere repetition of a physical aspect of the story prompts a request "Can you give me some more details?' as some degree of abstraction is required (see (Snowden, Gibbons et al. 2003)for a further discussion).

The emotional state responses in all cases have different valences (and in all cases can easily be determined from the story). The affective state of character A changes as the story progresses (as epistemic state also changes). If the participant gives a response which reflects the affective state of character A at the start of the story then the prompt "are there any changes in how s/he feels" is given. Responses of neutral valence such as "he is OK/ fine" are followed by the prompt- "can you be more specific about how they feel".

All responses were coded as correct or incorrect and converted to percentages, and the second order false belief further coded as above. A total score for the test was calculated taking the total number of correct responses across all questions. Where there was an incorrect answer to a control or inference question, the responses to the belief and emotion scores were excluded from the calculation of the final total score.

Rater reliability. Intraclass correlation coefficient between three independent raters were good (all >0.85). Any disagreements were settled by discussion and a group consensus reached.

6.4.3 Analyses

One way ANOVA or Kruskal-Wallis tests were used (depending on data characteristics) to examine group differences in performance on the various tests. To test the hypothesis that left sided amygdala lesions will more severely impair epistemic, and right sided lesions affective ToM reasoning, scores on tests requiring epistemic attributions (epistemic components of faux pas and conflicting belief and emotion) and tests assessing affective inferences (affective attributions in the faux pas and conflicting beliefs and emotions task) were combined. An index of 'content specificity' was calculated by using the equation (total epistemic attributions-total affective attributions)/ (total epistemic+ total affective attributions). This index thus expressed the difference in performance arising from the content of the task, adjusted for a measure of overall accuracy.

6.4.4 Results

Demographic and neuropsychological measures (table 6.1)

Missing data are reflected in the degrees of freedom. There were no significant differences on the basic neuropsychological measures between the clinical groups, who were significantly impaired relative to healthy comparison subjects on most measures. Demographic variables were similar for all the groups. Although the age of onset of habitual seizures was lower in the early amygdala damage than the late amygdala damage group, this did not reach statistical significance.

Table 6.1: demographic and neuropsychological characteristics.

	Early amygdala	Late amygdala	Clinical control group	Healthy control group	Significance
Sex (M;F)	7:8	7:4	6:8	22:35	$\chi^2(3)=2.4$ p=0.49
Age mean (s.d.)	35 (13)	33 (12)	27(7)	36 (12)	F(3,93)=2.1, p=0.11
Age of onset of epilepsy	12(9)	17 (12)	16 (9)	-	F(2,37)=0.85, p=0.44
Verbal IQ	98(13)	96(11)	94(15)	112 (9)	F(3,92)=18.1, p<0.001 EA***,LA***,CC***<NV
Performance IQ	102(14)	98(18)	99(18)	111 (6)	F(3,92)=6.5, p<0.001 LA*, CC**<NV
Logical memory I- scaled scores	7.4 (2.9)	8.3 (3.2)	8.0(2.6)	11.6 (2.6)	F(3,65)=11.8, p<0.001 EA***,LA***,CC**<NV
Brixton	5.6 (1.7)	5.9 (1.6)	6.1 (1.9)	7.1 (1.0)	F(3,64)=2.8, p=0.05
Hayling	5.6 (1.4)	5.0 (1.3)	5.4(1.9)	6.6 (1.5)	F(3,82)=4.5, p=0.006 LA*<NV

Key: EA=early amygdala damage, LA=late acquired amygdala damage, CC=clinical comparison group, NV=Normal volunteers (healthy comparison group)
Levels of significance; ***p<0.001, **p<0.01, *p<0.05

<u>False belief tasks (table 6.2).</u>

No subject made errors on the first order false belief questions. Four subjects with early amygdala damage and one late amygdala subject made errors on the second order false belief task.

<u>Happé's Strange Stories (table 6.2)</u>

There was a main effect of group in overall accuracy scores and post hoc analyses with Bonferroni correction confirmed significant differences between the early

amygdala damage group and the late amygdala, clinical and healthy comparison groups and between the clinical and healthy comparison groups. There was a group effect in the number of full mental state attributions made ($F(3,93)=6.7$ $p<0.001$). Post hoc analyses showed that the early amygdala group made significantly fewer full accurate mental state attributions than the late amygdala ($p=0.01$), clinical comparison ($p=0.06$) and healthy comparison groups ($p<0.001$)- illustrated in Figure 6.1. There were no significant differences in partial mental state ($F(3,93)=1.1$, $p=0.38$) or physical state attributions ($F(3,93)=0.8$, $p= 0.47$).

Metaphor and irony (table 6.2)

The results were highly skewed as subjects in late amygdala damage, and comparison groups made no errors. There was no effect of group on comprehension of metaphor. A Kruskal-Wallis test demonstrated a significant group difference in the comprehension of irony with pairwise comparisons showing the difference to be in the early amygdala relative to healthy comparison group ($Z=-3.1$, $p=0.001$).

Faux pas task (table 6.2)

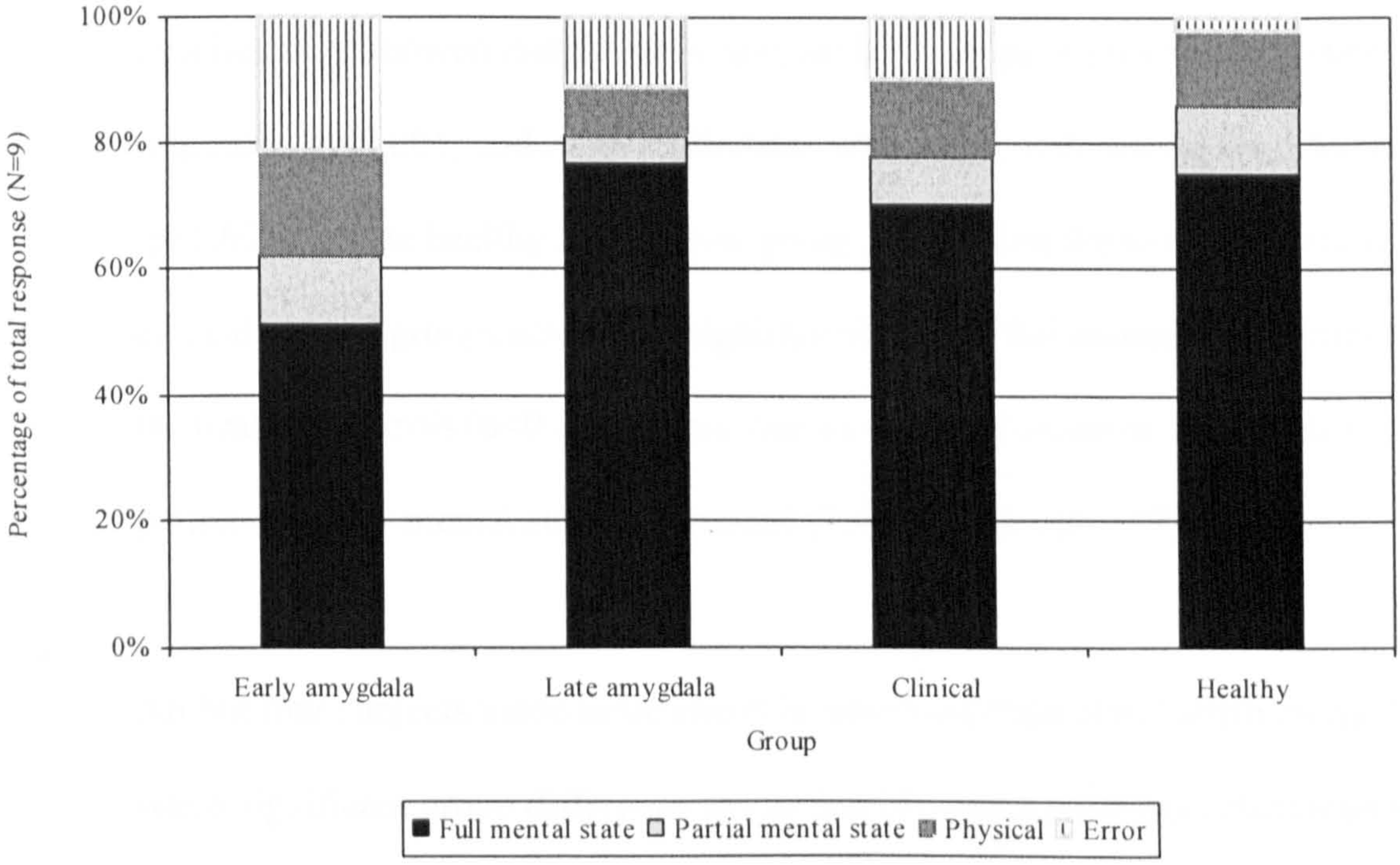
There were no group differences in the scores on control questions (with all groups displaying near perfect scores). There was a significant effect of group on the total number of correct detections and epistemic attributions, but not in affective attributions. Errors in the epistemic attributions all involved assuming that the faux pas had been made intentionally with the aim of upsetting the other protagonist in the vignette. There was a significant group difference in overall performance with pairwise Mann-Whitney comparisons showing that the early amygdala group were significantly impaired relative to the healthy comparison group ($Z=-3$, $p=0.002$) and

Table 6.2: results for each group on ToM tests

	Early amygdala (15)	Late amygdala (11)	Clinical comparison group (14)	Healthy comparison group (57)	ANOVA (and post hoc Bonferroni) or Kruskal-Wallis (and pairwise Mann-Whitney)
False belief					
Subjects making errors	4	1	1	2	χ^2=8.8, p=0.04
Happé- Strange Stories, metaphor and irony					
Strange stories mean (s.d.)- correct/incorrect	78 (13)	90 (7)	90 (12)	97 (6)	F(3,93)=22.6 p<0.001. EA<**LA,**CC,***NV, *LA, *CC<NV
Metaphor-median and (quartiles)	100	100	100	100	χ^2=4.1, p=0.25
Irony- median and (quartiles)	100 (70-100)	100	100	100	χ^2=15.3, p<0.001 EA<***NV
Faux pas					
Detection- median (quartiles)	100 (87-100)	100 (78-100)	100 (97-100)	100	χ^2=11.5, p=0.009 EA<***NV LA<**NV
Affective attributions	100 (64-100)	100 (75-100)	100 (97-100)	100	χ^2=6.7, p=0.08
Epistemic attributions	89 (67-100)	100 (67-100)	94 (86-100)	100	χ^2=14.4, p=0.002 EA<*CC, ***NV LA<*NV
Total score	89 (73-100)	100 (74-100)	98 (92-100)	100 (92-100)	χ^2=9.0, p=0.03 EA<CC (p=0.066), **NV
Conflicting beliefs and emotions					
Belief –true first order- median (quartiles)	100(96-100)	100 (96-100)	100 (96-100)	100	χ^2=3 , p=0.39
Belief- false second order	93 (67-100)	100 (86-100)	93 (86-100)	100	χ^2=14, p=0.003 ***EA, *LA, **CC <NV
Emotion- first order	83 (75-100)	85 (80-100)	100 (87-100)	100 (87-100)	χ^2=10.8, p=0.01 EA<CC, **NV, LA<*NV
Emotion-second order	85 (62-87)	85 (74-90)	100 (86-100)	100 (87-100)	χ^2=21.7 ,p<0.001 EA<**CC,***NV, LA<*NV

Key to table 6.2:
Level of significance of post hoc comparisons : *p<0.05, **p<0.01, ***p<0.001
EA= early amygdala damage; LA=late amygdala damage; CC=clinical controls; NV=Normal volunteers (healthy controls).

Figure 6.1: type of response in Happé's Strange Stories (a total of nine stories were used and the diagram illustrates the number of each type of response)



there was a near significant impairment relative to the clinical comparison group (Z=-1.84, p=0.066).

'Conflicting beliefs and emotions' task (Table 6.2).

One subject in the late and one in the early amygdala damage group failed to complete the test. There was no significant difference between the groups in the memory and inference questions. Performance on the first order true belief component was nearly at ceiling in all groups and a Kruskal-Wallis test showed no effect of group (see table 6.2) In the attribution of second order false beliefs, there was a significant difference between the groups in overall number of incorrect

responses ($F(3,91)=5.8$, $p=0.001$) with the early amygdala group making more such errors than the healthy comparison group ($p<0.001$). There was a significant group difference in the number of correct responses which contained a full mental state reference ($F(3,91)=9.4$, $p<0.001$) and physical state references ($F(3,91)=6$, $p=0.001$). Post hoc tests showed that the early amygdala group gave fewer mental state responses ($p<0.001$) and more attributions containing a physical state reference ($p=0.01$) than the healthy comparison group. In addition the late amygdala and clinical control groups also made significantly fewer full mental state attributions than the healthy controls ($p<0.01$). There was no effect of group on the number of partially correct mental state attributions ($F(3,91)=0.07$, $p=0.97$).

All but four subjects made more errors in emotional than belief attributions. There was a significant group difference in number of correct emotional attributions associated with both first and second order beliefs $F(3,91)=5.8$, $p=0.001$. Post hoc analyses showed that the early amygdala damage group made more errors in providing an emotion which was congruent with the belief state of the characters relative to both clinical ($p=0.02$) and healthy comparison groups ($p=0.003$).

Overall performance

A cumulative score reflecting in equal measure the scores on the four tests was calculated. There was a significant group difference ($F(3,93)=17.1$, $p<0.001$) with impairment in the early amygdala damage group relative to all the other groups (late amygdala damage group $p=0.02$, clinical control group $p=0.002$, and healthy control group $p<0.001$, Bonferroni corrected contrasts). There was a trend to impairment ($p=0.07$) in the late amygdala damage group relative to the healthy comparison group

only. Standardized effect sizes were also calculated, using Cohen's d , a statistical power analysis quantifying the size of the difference between groups[Cohen J 1992]. The index is interpreted as indicating a small between group difference for d=0.20, medium for d=0.50 and large for d>0.8. All clinical groups were substantially impaired relative to the healthy comparison group. The early amygdala group showed a large (d= 0.97), and the late amygdala group showed a small (d=0.13) difference with the clinical comparison group.

Table 6.3: Mean (s.d.) cumulative score on all ToM tests for each group. Effect sizes between each group are expressed as Cohen's d.

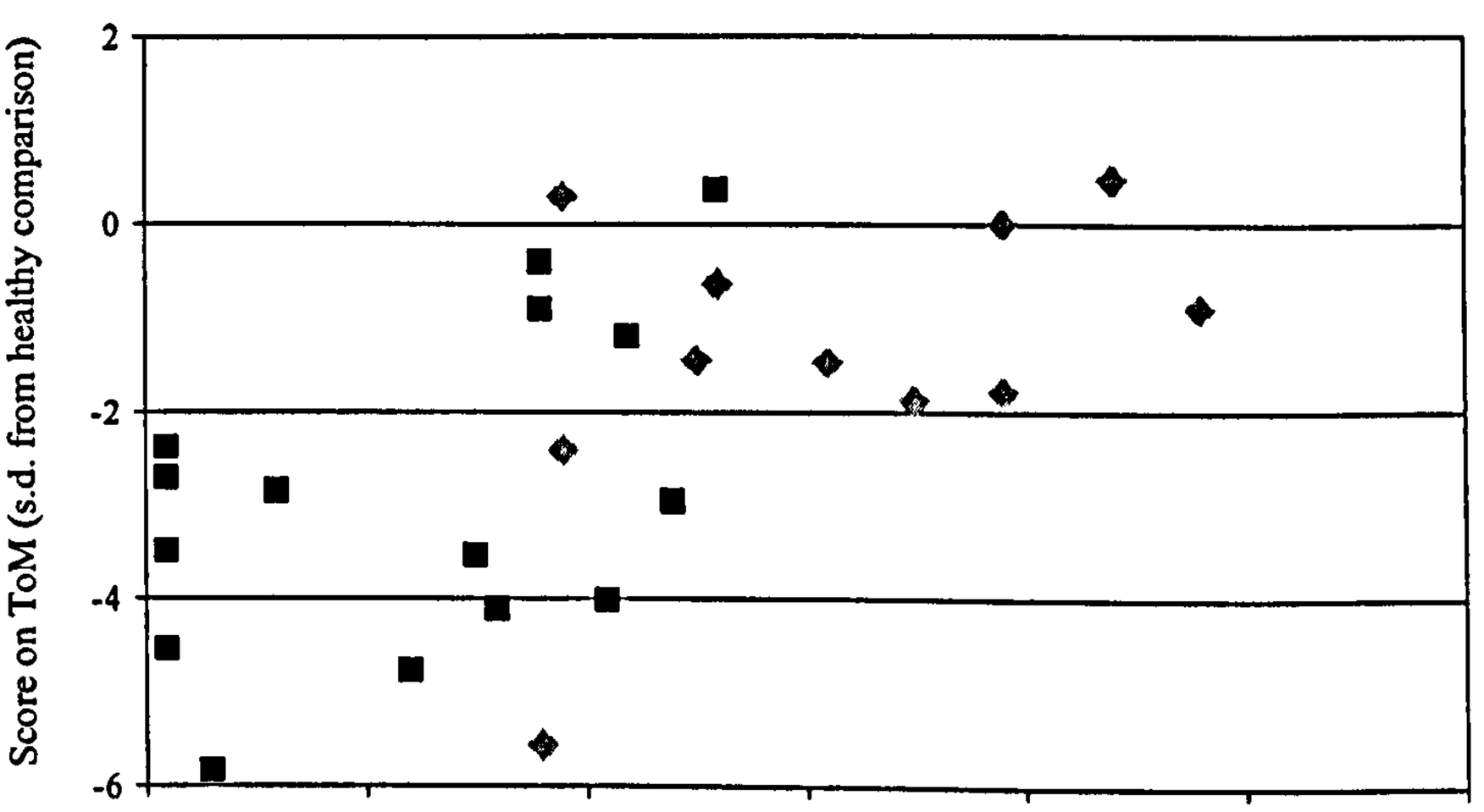
	Early amygdala Mean-81.4(10.3)	Late amygdala. Mean 89.3 (7.9)	Clinical controls Mean 90.4, (8.1)	Healthy controls Mean 94.9 (4.8)
Early amygdala	-	0.84	0.97	2.14
Late amygdala	-	-	0.13	1.04
Clinical comparison	-	-	-	0.81

<u>Relationship with the age of onset of damage to the amygdala</u> .

As discussed earlier the age of damage for the early amygdala group can be taken to be the age of onset of seizures which arise from the lesion. The age of damage to the amygdala in the late onset group is the age at which the patient underwent its surgical excision. As would be expected the age of damage to the amygdala in the 'early damage group' was in childhood (mean 12 yrs with s.d.9 yrs) and in the late amygdala damage group in adult life (mean 31 yrs with s.d. 10 yrs). This difference was highly significant (t= 4.8, p<0.001). There was a significant positive correlation between the age of onset of amygdala damage and the overall score (Spearman's rho= 0.64, p<0.001). Diagram 2 illustrates this correlation, with the overall score expressed as number of standard deviations from the mean of the healthy comparison

group. Within the early amygdala group alone, the correlation between age of onset of seizures and overall score was Spearman's rho=0.39, , p=0.16; and for the late amygdala damage group rho=0.40, p=0.23. All patients with a DNET who had an onset of epilepsy in childhood or early adolescence (less than 16 years) fell at least two standard deviations (s.d.) below the mean of the healthy comparison group. Four of the six patients who had a DNET associated with adult onset of seizures were less impaired (falling within two standard deviations of the healthy comparison group). Turning to the late amygdala damage group, two of the eleven subjects scored two standard deviations below the healthy comparison group. The age of onset of habitual seizures was not related to the degree of impairment in ToM reasoning in the late amygdala and clinical comparison groups (Spearman's rho =-0.08, p=0.68). Thus it is unlikely that an early age of onset of seizures per se, regardless of the location of the epilpetogenic focus, leads to deficits in ToM reasoning.

Figure 6.2. Relationship between the age of damage to the amygdala and overall score on the ToM battery (scores expressed as standard deviations from mean score of healthy comparison group).



■ = early amygdala damage group ◆ = late amygdala damage group

The relationship with general intelligence, memory and executive function (table 6.4).

There were modest positive correlations within each group between these variables and the overall measure of performance on ToM tests. We thus reanalysed the data with these measures as covariates. The significant difference between the early amygdala damage group and all other groups held in pairwise comparisons between the individual groups (with a Bonferroni correction and $p<0.05$) after co-varying for executive function, logical memory and general intelligence, both singly and in combination. The significant difference between the late amygdala damage and healthy and clinical control groups did not remain after adjustment for differences in executive function, memory and IQ between the groups.

Table 6.4: Pearson correlations between ToM tests (overall score) and IQ, logical memory and executive function.

Group	VIQ	PIQ	Logical memory	Brixton	Hayling
Early amygdala	0.43	0.21	0.04	0.35	0.56
Late amygdala	0.35	0.29	0.12	0.53	0.42
Clinical controls	0.06	0.46*	0.50*	0.25	0.21
Healthy controls	0.22	0.22	0.39*	0.11	0.12

Key: *=significant at unadjusted $p<0.05$.

The effect side of lesion and gender.

As can be seen from table 6.5 there were no significant gender differences within each group, although in the early and late amygdala damage group and the healthy control group, females tended to perform slightly better. Collapsing the results for the

cumulative index the genders did not differ (female mean 91.2, SD.8.8; male mean 92.1, male mean 92.1, SD 7.5: t(85)=0.48, p=0.63).

Table 6.5. Results in overall performance on ToM tests by gender

	Early amygdale	Late amygdala	Clinical controls	Healthy controls
Male -median (quartiles)	79 (75-85)	90 (84-97)	94 (86-100)	96 (93-98)
Female – median score (quartiles)	82 (76-91)	91 (87-95)	90 (84-96)	96 (93-98)
Mann-Whitney test	Z=-0.69, p=0.49	Z=-0.19, p=0.85	Z=0.1.1, p=0.25	Z=0.01, p=0.99

For the cumulative score subjects with right sided lesions had a mean score of 86.7 (s.d. 8) which did not differ significantly from the mean score of 86.7 (s.d.11) for the subjects with left sided lesions (t(38)=0.01, p=0.98). For the early amygdala damage group, there was also no significant difference between those with right (median score 79) and left sided damage (median score 82), (Mann-Whitney, Z=0, p=1.0).

An index of content specificity was calculated to give a measure of the relative performance on epistemic versus affective ToM reasoning. The side of damage and location of damage (24 amygdala damage and 14 non-amygdala damage) were then entered into a 2x2 ANOVA with the index as the dependent variable. There was no main effect of side (F(1,34) =1.1, p=0.3) or location of damage (F(1,34)=1.3, p=0.26 and no interaction (F(1,34) =1.0, p=0.32).

6.5 Discussion

6.5.1 Key findings

The study demonstrated deficits in advanced tests of reasoning about the mental states of others among subjects with lesions of amygdala arising early in development, particularly if associated with childhood onset of seizures. By contrast, subjects with lesions of the amygdala acquired in adult life showed no significant impairment in theory of mind tasks relative to a clinical comparison group of subjects with lesions which spared the amygdala. This pattern of deficits held after co-varying measures of general intelligence, executive function and verbal memory. There was no effect of side of damage or gender on overall performance. There was also no evidence of an interaction between the side of amygdala damage and impairment on specific types of mental state attribution (epistemic versus affective).

In the primary analyses the developmental stage of amygdala damage was defined pathologically; early amygdala damage subjects had a DNET and late amygdala damage subjects had a histologically normal amygdala excised in adulthood. Given the uncertainly about the exact age at which DNETs arise we include a complementary method of dating the age of the amygdala DNETs - taking the age of onset of the lesion to be the age of onset of associated epilepsy. Adopting this method, all subjects with amygdala DNETs associated with a childhood or early adolescent onset of seizures (less than 16 years) had impaired ToM reasoning compared to healthy subjects. By contrast only two subjects with damage to the amygdala which arose in adult life due to surgery showed marked ToM impairments. This raises the possibility of a sensitive period in development of ToM reasoning which extends to late childhood, during which damage to the amygdala leads to

impairments, particularly if the damage is so severe as to be clinically and neurophysiologically apparent. Research into healthy children suggests that the ability to perform the faux pas task is acquired in late childhood (between the ages of 7-11), several years after children reliably pass first and second order false belief ToM tests (Wellman, Cross et al. 2001). Deficits in the early amygdala damage group are only apparent in the developmentally advanced tests of ToM such as the faux pas, implying that such damage is associated with a degree of developmental delay, rather than developmental arrest.

The findings are compatible with deficits shown by subjects SM who has bilateral amygdala damage which is likely to have started early in childhood. When asked to describe the Heider and Simmel film of animated shapes, which is normally seen as full of social content, she used language devoid of mental state terms, and used entirely geometric terms(Heberlein and Adolphs 2004). This occurred despite intact visual perception and declarative social knowledge. Interestingly the deficits held when she was compared to eight subjects with orbitofrontal damage who used entirely normal language in the task- a striking finding in support of a very specific role for the amygdala. On the basis of SM's intact store of social knowledge the authors argue that it is unlikely that the early amygdala damage resulted in a failure to acquire requisite social experiences and knowledge. Rather they argue that the amygdala has a role in automatically triggering its retrieval, particularly when visual stimuli are being processed. Our finding of broad deficits in verbal theory of mind tasks in subjects with unilateral damage suggests that the amygdala's role in ToM is unlikely to be confined to the visual triggering of stored information.

We can only speculate about the possible cognitive origins of the delay in theory of mind skills that we find in our unilateral amygdala damage group. The amygdala appears to be a pivotal structure in supporting some of the earliest precursors of ToM reasoning. Lesion and functional MRI studies both suggest it plays a critical role in the monitoring the direction of eye-gaze necessary to engage in shared attention and detecting the emotional states of others on the basis of their appearance (Baron-Cohen, Ring et al. 1999; Morris, deBonis et al. 2002; Adams, Gordon et al. 2003; Zald 2003). By disrupting such precursors of ToM reasoning, early damage to the amygdala may thus slow the trajectory of the development of the theory of mind, in many cases preventing subjects reaching the most advanced stages of the skill. The late amygdale damage group, by contrast, had intact bilateral amygdala early in development and thus may have had a normal early interest in social interaction and eye gaze monitoring abilities. This may explain the pattern of deficits found in the early amygdala damage group of generally intact, but not perfect, basic ToM function, and impaired, qualitatively anomalous performance on the more complex tasks of ToM such as the faux pas and comprehension of irony. This explanation links the role of the amygdala in emotional perception with a role in ToM reasoning. Other possible mechanisms, most notably a failure in the processes which enhance the storage and retrieval of emotionally salient memories may also result in a paucity of social learning.

Early damage to the amygdala has been linked explicitly to the later development of autism which arguably has impaired ToM reasoning as its core neurocognitive deficit. It is interesting that the quality of the correct responses given by the subjects with early amygdala damage is reminiscent of those given by people who have autism

(Happe 1994; Jolliffe and Baron-Cohen 1999). For example in Happé's strange stories and the novel conflicting belief and emotions tasks, the subjects with early amygdala lesions tended to give fewer correct answers couched in explicitly correct mental state references. This is suggestive of impairment in spontaneously and automatically 'mentalizing' when faced with the task of interpreting the actions of other agents. Similarly participants with early amygdala damage frequently made inappropriate affective attributions in the conflicting belief and emotion test, even when they made the correct epistemic attributions. This is reminiscent of the finding by Baron-Cohen et al that subjects with autism find the comprehension of emotional states particularly difficult when they are associated with belief states (rather than, for example, those evoked by a certain situation) (Baron-Cohen 1991). Given the similarities between these responses and those given by subjects with autism and Asperger's syndrome to similar stories, we would interpret such answers as reflecting an inability to reason accurately about the mental states of others. Thus the impairments in ToM reasoning are qualitatively similar to those often reported in autism and Asperger's and as such as are consistent with the idea that the amygdala plays a role in the aetiology of these neurodevelopmental disorders.

There are several possible interpretations of the lack of deficits in the late amygdala damage group. Firstly it could be argued that the amygdala may be necessary for the performance of ToM reasoning and that just one intact amygdala is sufficient for this processing. There are several instances of functional reduplication within the brain whereby the loss of one structure is readily compensated for by the presence of its homologue. If this were the case, then deficits in ToM reasoning would only be present in subjects with late acquired damage only if both amygdalae were affected-

such as that found in subjects described by Stone and colleagues, all of whom have some impairment in ToM reasoning tasks (Stone, Baron-Cohen et al. 2003). This position would also explain the functional imaging reports of amygdala activation during putative ToM reasoning tasks (Baron-Cohen, Ring et al. 1999). However, these lesion and functional imaging studies are open to criticism. Firstly, two of the bilateral subjects (SE and DR) in the Stone study had damage to regions extending beyond the amygdala which may have contributed to the impairments in ToM tasks (Stone, Baron-Cohen et al. 2003). One of the subjects (DR) had marked impairments in executive function which alone could have led to failure on many of the tasks and may also have had early developmental damage to one amygdala. Turning to the functional imaging studies, Frith and Frith have noted that the tasks which report amygdala activation use stimuli such as the human face and eye region, which may recruit the amygdala even in the absence of a clear ToM component (Frith and Frith 2003). It is debatable the extent to which the simple attribution of a mental state to another person on the basis of their appearance is truly a 'ToM' activity which some argue must entail a meta-representational component. None of the tasks which we employed which more clearly assess ToM reasoning have demonstrated amygdala activation during functional MRI. Although the evidence from our study cannot rule out the possibility of an 'on-line' role for the amygdala we feel it weakens the plausibility of this position. In other domains of social cognition such as moral reasoning, a similar relationship between impairments and the age of acquisition of a lesion has been reported. A comparison of the effects of early and late acquisition of lesions to the prefrontal cortex found more pervasive impairments in moral reasoning among two subjects with early compared to late prefrontal cortex damage (Anderson, Bechara et al. 1999).

6.5.2 Limitations

Several important cautions must be considered in this study. Firstly, the impairment demonstrated by the early amygdala damage group might not be considered severe: the majority of subjects passed the standard first and second false belief ToM tests and were mostly intact in the detection of irony (which is in essence a test of second order ToM reasoning). Deficits were only apparent in the more advanced tests of ToM and even in these tests the deficits in absolute terms were not great. It would therefore be important to place these impairments in the context of other groups who are also thought to exhibit ToM deficits. This is limited by the lack of a standardised battery of ToM tests but some comparisons are possible from several studies which have used Happé's Strange Stories (table 6.5)

Table 6.5: Effect sizes (Cohen's d) of the difference between clinical groups and relevant comparison groups reported in different studies using Happe's Strange Stories.

Study	Clinical group	Comparison group	Cohen's d
Current study	Early amygdale	Healthy subjects	2.14
	Early amygdale	Clinical comparison	0.97
[Happe 1994]	Subjects with high functioning autism*	Age-matched healthy subjects	1.23
	Subjects with autism who failed basic ToM tests	Age-matched healthy subjects	2.25
[Jolliffe and Baron-Cohen 1999]	Subjects with high functioning autism	Age-matched healthy subjects	1.41
	Subjects with Asperger's syndrome	Age-matched healthy subjects	1.24
[Happe *et al.* 1999]	Right hemisphere CVA	Age-matched healthy subjects	1.35

Key to table 6.5.*=high functioning autism refers to the ability to pass first and second order false belief tasks.

On the Happe test of advanced ToM processing the deficits in the early amygdala group relative to a healthy comparison group are of a similar magnitude (reflected in similar large effect size) to those shown by subjects with high functioning autism and Asperger's syndrome and subjects with extensive right hemisphere damage due to strokes. In the faux pas test, a direct comparison is possible with Stone's original study (Stone, Baron-Cohen et al. 1998). Patients with orbitofrontal damage had an estimated median score of 86% (interquartile range 76-96%), compared with performance at or near ceiling for subjects with dorsolateral prefrontal cortex lesions and healthy comparison subjects. These scores are similar to the median score of the early amygdala damage group of 89% (interquartile range 73-100%). Studies with subjects with autism and the frontal variant of fronto-temporal dementia suggest that the deficits in these groups on the faux pas test are more severe, but direct comparisons are difficult due to methodological differences (Baron-Cohen, O'Riordan et al. 1999; Gregory, Lough et al. 2002). These findings suggest that the early amygdala group have impairments in the advanced tests of ToM which are comparable to subjects with high functioning autism and Asperger's syndrome and those with lesions of other candidate components of the ToM neural circuitry. Equally, the impairments in the subjects with early amygdala DNETs are not as severe as those found among most people who have autism, emphasising the fact that we view early amygdala damage as only one of the contributors to a delay in the development of ToM reasoning.

A second important caveat is the presence of almost entirely normal ToM function in some of the subjects in the early amygdala group. Why were these subjects unimpaired? Firstly, there is the possibility of a type 1 error: although the probability of this is low given the effect sizes reported. Secondly, the presence of intact performance in the face of amygdala damage raises the possibility that the amygdala may not be a core component of the development of ToM reasoning and may provide, instead domain general support for ToM reasoning. By this reasoning, compensation for early damage to the amygdala may occur more readily as it is not a core component of ToM reasoning, and thus subjects with amygdala damage may not always demonstrate clear ToM impairments. If this were so, deficits would only be evident in tests which relied on the domain general functions of the amygdala. While this is not excluded by our study it is unlikely as the impairment of the early amygdala damage group relative to the other groups held after co-varying for a wide range of measures of general cognitive function. However the case for a core contribution of the amygdala would be strengthened by the demonstration of deficits on a wider battery of tests, less reliant on verbal processing and comprehension than those used in the current study.

Finally, it is notable that all the unimpaired subjects with amygdala DNETs had an adult onset of epilepsy (see figure 2). This may reflect the presence of a DNET which is less disruptive to amygdala neuronal integrity leading both to a later age of onset of epilepsy and less impairment in the development of ToM. This is reminiscent of Hughlings Jackson's hypothesis that a discharging or epileptogenic focal lesion may inhibit neuronal re-organisation and compensation more than focal lesions which are 'non-discharging'(Jackson 1996). Thus patients who have a clinically silent DNET

throughout early childhood may have been better able to compensate for the presence of an early focal lesion of the amygdala. We would however predict that such compensation may often not be complete, which would account for the deficits found in one subject with an amygdala DNET who had adult onset of seizures. Additionally we might expect that on more subtle measures of ToM processing such as reaction times or the quality of responses, differences may be apparent. As the age of onset of habitual seizures was not significantly correlated with the degree of impairment in ToM reasoning in the late amygdala and clinical comparison groups (whose epileptogenic lesions lie outside the amygdala) it is unlikely that an early age of onset of seizures per se, regardless of the location of the epilpetogenic focus, accounts for the deficits in ToM reasoning.

A major potential drawback is the difference in extent of extra-amygdala damage in the early onset and late onset groups, with the latter group generally having more extensive involvement of other anterior temporal lobe structures. We did not include a control condition of stories which had a non-mental state content, which may help in excluding the possibility that impairment arises from factors unrelated to ToM reasoning such as the ability to form an integrated narrative from each vignette. However, the lack of a significant correlation between measures of general intellectual ability, executive function and ToM performance and the intact performance on the comprehension and inference conditions in the tests makes an explanation in these terms unlikely. Additionally, the vignettes for assessing the comprehension of irony and metaphor were structurally identical, yet deficits were only present in the interpretation of irony which relies on intact ToM reasoning.

Although the focus of the study was on the amygdala some participants had damage to other structures which are held to mediate ToM reasoning, such as the temporo-parietal junction. This area is activated in fMRI studies tapping this domain (Frith and Frith 2003; Saxe and Wexler 2005), and ToM reasoning impairment has been reported in adults with acquired lesions of the region (Samson, Apperly et al. 2004). Only one subject in our study had a lesion in this region and she made relatively few errors on the tasks, performing at the mean level for the clinical control group. Future work could examine more systematically the effects of lesions in these specific areas.

The frontal lobes, particularly the ventromedial prefrontal cortex, are also implicated in theory of mind by most, but not all, lesion and functional imaging studies(see for example, (Bird, Castelli et al. 2004; Sabbagh 2004; Shamay-Tsoory, Tomer et al. 2005). Some of these studies include patients with posterior brain damage as a clinical control group, some of whom may have amygdala damage, and generally report no deficits in this group relative to healthy controls. However, as most of the 'posterior damage' subjects included in these studies had acquired damage in adulthood, even if the amygdala was involved, we would not predict deficits.

6.6 Conclusion

In conclusion we found that lesions of the amygdala which arise early in development and act as epileptogenic foci in childhood were associated with deficits in ToM reasoning. Subjects who sustained surgical damage to a previously normal amygdala in adult life were intact in most tests of ToM relative to a clinical comparison group. These impairments cannot be reduced to executive dysfunction, which was not

marked in the subjects with amygdala lesions and which did correlate strongly with overall performance. The study provides initial evidence compatible with the postulation of the amygdala as part of the neural system which supports the development of ToM reasoning.

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Chapter 7: Self-reported empathic skills.

7.1 Summary

We assess the impact of amygdala lesions arising at different developmental stages on a self-report measure of empathy (the Empathy Questionnaire –EQ), indirectly testing the hypothesis that the amygdala is a necessary structure for the development of these skills. Contrary to our predictions, participants with amygdala lesions – either arising early or late in development - did not show deficits in self-rated empathic skills relative to a group of clinical control subjects. There was a high correlation between the ability to discriminate between the basic emotions and EQ scores, suggesting that loss of this fundamental skill may weaken the foundation for later development of empathic abilities.

Some of the findings of this study have been published in *Psychological Medicine* (with Dr E. J. Lawrence as first author, and a copy of the paper is included at the end of the thesis).

7.2 Introduction

In the previous chapters deficits associated with amygdala lesions have been demonstrated in emotion recognition, reasoning about mental states and remembering affectively charged material. We now address two questions. Firstly, do these skills relate to each other? We would predict that if all are mediated to some degree by the amygdala then damage to the structure would impair performance in all groups to a similar extent. Secondly, do these deficits affect empathic skills?

There are several lines in the literature which suggest that amygdala damage may be linked with disorders characterized by poor empathic skills- particularly autism. These are reviewed elsewhere(Howard, Cowell et al. 2000; Jolliffe and Baron-Cohen 2000; Baron-Cohen 2004; Pelphrey, Adolphs et al. 2004), but in brief a link between amygdala damage and autism is supported by the presence of macroscopic and microscopic anomalies of the amygdala in autism. This includes inconsistent findings of alteration of amygdala volumes on volumetric studies not only among people with autism, but also Asperger's syndrome and perhaps unaffected first degree relatives(Rapin and Katzman 1998; Giedd, Shaw et al. 2006). In functional imaging studies, anomalous amygdala activation has been noted in people with Asperger's syndrome and autism during the passive viewing of faces, particularly those which are expressing emotions, (Critchley, Daly et al. 2000) and during the recognition of complex social expressions (Baron-Cohen, Ring et al. 1999). More indirect evidence comes from the association between amygdala volume across species and size of kin networks: the larger the amygdala the more social the animal(Emery, Lorincz et al. 1997). Additionally there is extensive evidence that lesions of the amygdala affect social behaviour in primates, since the early demonstrations of the drastic alterations of social behaviour following bilateral removal of the temporal lobe (Kluver and Bucy 1939). More selective lesions restricted to the amygdalohippocampal complex in newborn rhesus monkeys induce withdrawal and loss of interest in social contact and decreased amounts of eye contact(Aggleton JP 1993; Resende, Chain-Fourney et al. 2002). These abnormal behaviours have obvious parallels to the social difference seen in people with autism.

There are also some similarities between subjects with amygdala lesions and the social and communication anomalies seen in autism, much of which has been already reviewed. For example, subject SM who has bilateral amygdala damage makes highly abnormal judgments on the trustworthiness and approachability of others(Adolphs, Tranel et al. 1998). A patient BM with a congenital left amygdala lesion (thought to be a DNET) has been described who both had Asperger's syndrome and theory of mind deficits despite intact executive function(Fine, Lumsden et al. 2001). Systematic investigation of the consequences of amygdala lesions on social behaviour in humans has been lacking, although several investigators comment on the outgoing, trusting and perhaps disinhibited personalities of those with bilateral amygdala damage(Adolphs 2002)

We thus examined whether the deficits in emotion recognition, theory of mind reasoning and emotional memory we have demonstrated in patients with amygdala damage- particularly early amygdala damage- extends to the quality of being empathic.

A discussion of the meaning of empathy is beyond the scope of this thesis, and has been reviewed extensively. In a recent formulation, empathy has been defined as comprising a cognitive component, in the ability to understand and predict someone else's mental state, and an affective component, namely the ability to experience an appropriate emotion as the result of apprehension of someone else's mental state(Baron-Cohen and Wheelwright 2004).

The assessment of empathy is complex. One strand has used self-report measures of empathic skills, to some degree assuming that people can reflect upon their experiences of empathizing, much as they can reflect upon their emotional experiences. Several of the most widely used self-report scales are listed below in table 7.1.

Table 7.1: self-report measures of empathy

	Reliability	Validity	Factor analysis
Questionnaire measure of emotional empathy (Mehrabian and Epstein 1972)	Split half reliability .84	*predicts aggressive behaviour *low correlation with scores on social desirability scale	*emotional contagion *emotional responsiveness *appreciating feelings of distant others
Empathy Scale (Hogan 1969)	Split-half reliability (0.84)	*correlates with measures of communication competence, moral maturity and effective social functioning	*even-tempered disposition *sociable interpersonal style *humanistic socio-political attitudes
Interpersonal reactivity index (Davis 1980)	Test –retest reliability r=.81 Split-half reliability .78	*none	*empathic concern *perspective taking *fantasy (ability to identify with fictional characters) *personal distress

A recurrent limitation is the lack of construct validity for these measures, which often relied on correlations with behavioural tendencies such as aggression or moral reasoning. While these behaviours may reflect empathy, they contain multiple other non-empathic components. Many of the items in each scale may tap processes that are not empathic. For example, the factor of 'humanistic socio-politico concern' contains items which have only tenuous links to empathy such as: 'it is the duty of a

citizen to support his country'. Similarly, items falling under the factor of fantasy (i.e. the ability or the tendency to identify with fictional characters) also lack a clear link with empathy.- 'I daydream and fantasize with some regularity about things that might happen to me.'

A recent addition to the self report scales is the Empathy Questionnaire by Baron-Cohen and colleagues(Baron-Cohen and Wheelwright 2004). The measure was explicitly designed to have a clinical application and be sensitive to a lack of empathy as a feature of psychopathology. There are 60 items including 20 filler items; responses are given on a four point scale, ranging from 'strongly agree' to 'strongly disagree'. The scale was initially validated on 197 healthy control volunteers and 90 people with Asperger's syndrome or high functioning autism. It was shown to reliability distinguish between the clinical and control groups, suggesting some degree of construct validity, in addition to putative clinical utility. In addition the measure was found to be correlated with a Friendship questionnaire designed to measures intimacy in relationships(Baron-Cohen and Wheelwright 2003). We also recently demonstrated modest correlation between scores on the EQ and the 'Eyes' test (Lawrence, Shaw et al. 2004). In addition we have shown that the task has good concurrent validity, with significant, if modest correlations between total EQ scores in 25 healthy volunteers and the 'empathic concern' and 'perspective taking' subscales from the Interpersonal Reactivity Index (Davis 1980). The EQ also has good test-retest validity over a period of one year, and robust internal validity. In an exploratory factor analysis, three factors were extracted which accounted for 41% of the total variance. The first factor, labeled 'cognitive empathy' includes items that measure the appreciation of affective states (e.g. 'I can tell if someone is masking

their true emotion') epistemic states (e.g.' I find it easy to put myself in somebody else's shoes') and desire based states (e.g. 'I can easily work out what another person might want tot talk about'). The second factor was labeled 'emotional reactivity' as the items loading onto this factor reflect the tendency to have an emotional reaction in response to another's mental state (e.g.'seeing people cry doesn't really upset me' or 'I tend to get emotionally involved with a friend's problems'). The final factor of 'social skills' contained items such as:'I find it difficult to judge whether something is rude or polite'. Such items are in part indicative of a lack of intuitive social understanding and are reliant on a knowledge of social rules. Of note, this was the only factor which females did not have significantly higher scores. Thus the first and second factors map well onto traditional concepts of cognitive and affective empathy, and the third factor provides a measure of applied empathy.

Neural basis of self-rated empathic skills.

There are a plethora of case reports of changes in social sensitivity and skills following damage to the frontal lobe lesions (Stuss and Benton 1986; Blair and Cipolotti 2000). However, only one study has examined the neural basis of a self-report measure of empathy (the Interpersonal Reactivity Index) (Shamay-Tsoory, Tomer et al. 2003). This study found that patients with prefrontal damage, particularly of the ventromedial portions, had a significantly lower overall empathy score than a group of healthy controls and patients with posterior lobe damage, who did not differ significantly from one another. Further, empathy scores among patients with ventromedial damage correlated with measures of theory of mind reasoning, whereas empathy scores in patients with dorsolateral damage correlated with measures of cognitive flexibility. To date, no study has examined the possibility that

amygdala damage may also result in decreased empathic skills, as assessed by self-report.

7.3 Hypotheses.

Firstly, we predicted that there would be a correlation between performance on the various tasks we have shown to be sensitive to amygdala damage. Secondly, we predicted that lesions of the amygdala would be associated with lower empathic skills and abilities, as assessed by self report. Further, we hypothesized that early lesions of the amygdala would be associated with greater deficits in empathic skills. Finally we examined if scores on a self report measure of empathy correlated with scores on emotion recognition and theory of mind reasoning, which would support the validity of self-report scales of empathy as a research tool.

7.4 Methods

7.4.1 Participants

In estimating the correlation between the various tasks data were available on between 39 and 45 subjects (reflected in degrees of freedom). The EQ was completed by thirteen subjects in the early amygdala damage group, (five with right and eight with left sided damage),.and nine subjects in the late amygdala damage group. There was only one participant with right sided damage in the late amygdala damage group and so this group was combined in all analyses regardless of side of damage. Twelve clinical controls, (three with right sided and nine with left sided damage) and sixty healthy controls, without any history of psychiatric or neurological disorders also completed the EQ. A large number of subjects had participated in other studies in the department into the validity and reliability of the EQ, in collaboration with Dr E J Lawrence (Lawrence, Shaw et al. 2004).

7.4.2 Tasks.

The EQ has been described above. In brief it contains 60 items, 40 which pertain to empathy and 20 filler items. Each item has four possible responses. 'strongly agree/agree somewhat/disagree somewhat/disagree strongly'. Half the items were framed in a positive manner: for example, 'I am good at telling when someone else wants to enter a conversation', and half in a negative manner: 'I can't always tell when someone is hiding their true emotions'. For positively framed items, two points were given for a 'strongly agree' empathic response; one point for a 'agree somewhat' response; zero points for either a 'disagree strongly' or 'disagree somewhat' response. Negatively framed items were scored in the reverse manner. Cumulative total of all 40 items and for each three factors were calculated and converted to percentages to allow within subjects analyses.

Correlations were calculated between total and factor EQ scores with theory of mind scores, emotion recognition indices, executive functioning (Hayling and Brixton) and IQ.

7.5 Results

7.5.1 Correlations between the tasks.

Spearman's rank correlations were calculated on the scores of the various tasks. No adjustment was made for multiple comparisons. For emotion recognition, the discrimination index for all the basic emotions combined was used (the difference between the mean overall congruent or 'correct' intensity ratings less the mean incongruent ratings) as well as the overall accuracy score in the 'Reading the mind in

the eyes task'. For theory of mind the cumulative index was used, reflecting performance on the Happe Strange Stories, faux pas, false belief tasks and the conflicting belief and emotions task (for its calculation see chapter 6).

As shown in Table 7.3 , across all groups there was significant correlation between the two expression recognition tasks. The recognition of more complex, but not basic, expressions, was also correlated with the theory of mind reasoning scores. The theory of mind reasoning and emotional enhancement of memory also correlated significantly. Verbal IQ was correlated with all tasks except the emotional enhancement of memory, and the Hayling task scores showed more modest correlations with the tasks.

Table 7.3 Correlations between the tasks used in the studies

		Complex expressions	ToM	Emotional memory	Verbal IQ	Haylings
Basic emotions-discrimination index	Correlation	.346*	.230	.067	.365*	.083
	Sig.	.020	.115	.665	.011	.574
	N	45	48	44	48	48
Complex expressions	Correlation		.420**	.126	.431**	.269
	Sig.		.002	.404	.001	.056
	N		54	46	53	51
ToM	Correlation			.282*	.359**	.191
	Sig.			.047	.006	.159
	N			50	58	56
Emotional memory	Correlation				.134	-.073
	Sig.				.353	.622
	N				50	48
Verbal IQ	Correlation					.311*
	Sig.					.020
	N					56

Controlling for verbal IQ and Hayling scores, using partial correlation, removed the significant correlations between the emotion recognition tasks, and reduced the correlation between the ToM and emotional memory index to a trend (r=0.27, p=0.09). The correlation between the recognition of complex expressions and ToM) increased slightly (r=-.48, p=0.002). Spearman's rank correlations were examined within each group, and were generally very modest, and none reached significance-

Table 7.4.

Table 7.4 Correlations within each group.

Group				Complex expression recognition	ToM score	Emotional memory index
Early amygdala		Basic emotions-discrimination index	Correlation Coefficient	-.063	.077	.119
			Sig. (2-tailed)	.845	.803	.713
			N	12	13	12
		Complex expression recognition	Correlation Coefficient		.187	.063
			Sig. (2-tailed)		.522	.845
			N		14	12
		ToM score	Correlation Coefficient			-.060
			Sig. (2-tailed)			.845
			N			13
Late amygdala		Basic emotions-discrimination index	Correlation Coefficient	-.300	.314	.000
			Sig. (2-tailed)	.624	.544	1.000
			N	5	6	5
		Complex expression recognition	Correlation Coefficient		.075	-.600
			Sig. (2-tailed)		.847	.208
			N		9	6
		ToM score	Correlation Coefficient			-.143
			Sig. (2-tailed)			.736
			N			8
Clinical controls		Basic emotions-discrimination index	Correlation Coefficient	.135	.150	.152
			Sig. (2-tailed)	.710	.659	.676
			N	10	11	10
		Complex expression recognition	Correlation Coefficient		.240	-.009
			Sig. (2-tailed)		.431	.979
			N		13	11
		ToM score	Correlation Coefficient			-.151
			Sig. (2-tailed)			.640
			N			12

Healthy controls		Basic emotions-discrimination index	Correlation Coefficient	.357	.116	-.082
			Sig. (2-tailed)	.146	.647	.754
			N	18	18	17
		Complex expression recognition	Correlation Coefficient		.211	-.265
			Sig. (2-tailed)		.401	.303
			N		18	17
		ToM score	Correlation Coefficient			.248
			Sig. (2-tailed)			.338
			N			17

7.5.2 EQ results.

Demographic characteristics of the participants who completed the EQ are given in Table 7.5. The groups differed in verbal IQ ($F(3,85)=12.4$, $p<0.001$, with all clinical groups having a significantly lower IQ ($p<0.05$) than the healthy controls. There was a near significant difference in age ($F(3,90)=2.6$, $p=0.06$), but no significant pairwise group differences. The groups did not differ significantly in gender composition $\chi^2=6.4$, $p=0.88$.

Table 7.5 Demographic characteristics of participants in EQ study (means (SD)

	Age (SD)	IQ	Gender
Early amygdala	36(12)	99(14)	5:8
Late amygdala	35(9)	100(14)	4:5
Clinical control	26(6)	93(15)	6:6
Healthy controls	34 (11)	110(7)	23:37

In overall EQ scores (expressed as a percentage score) there was a near significant group difference, $F(3,90)=2.5$, $p=0.07$, but no significant pairwise group differences in post hoc emerged in analyses with Bonferroni correction- Table 7.6.

Table 7.6 Total EQ scores (expressed as percentage)

	N	Mean	SD	Minimum	Maximum
Early amygdala	13	50.5	16.2	22.5	77.5
Late amygdala	9	54.2	19.9	31.3	87.5
Clinical controls	12	52.0	16.6	25.0	77.5
Healthy controls	60	62.0	17.5	16.3	97.5

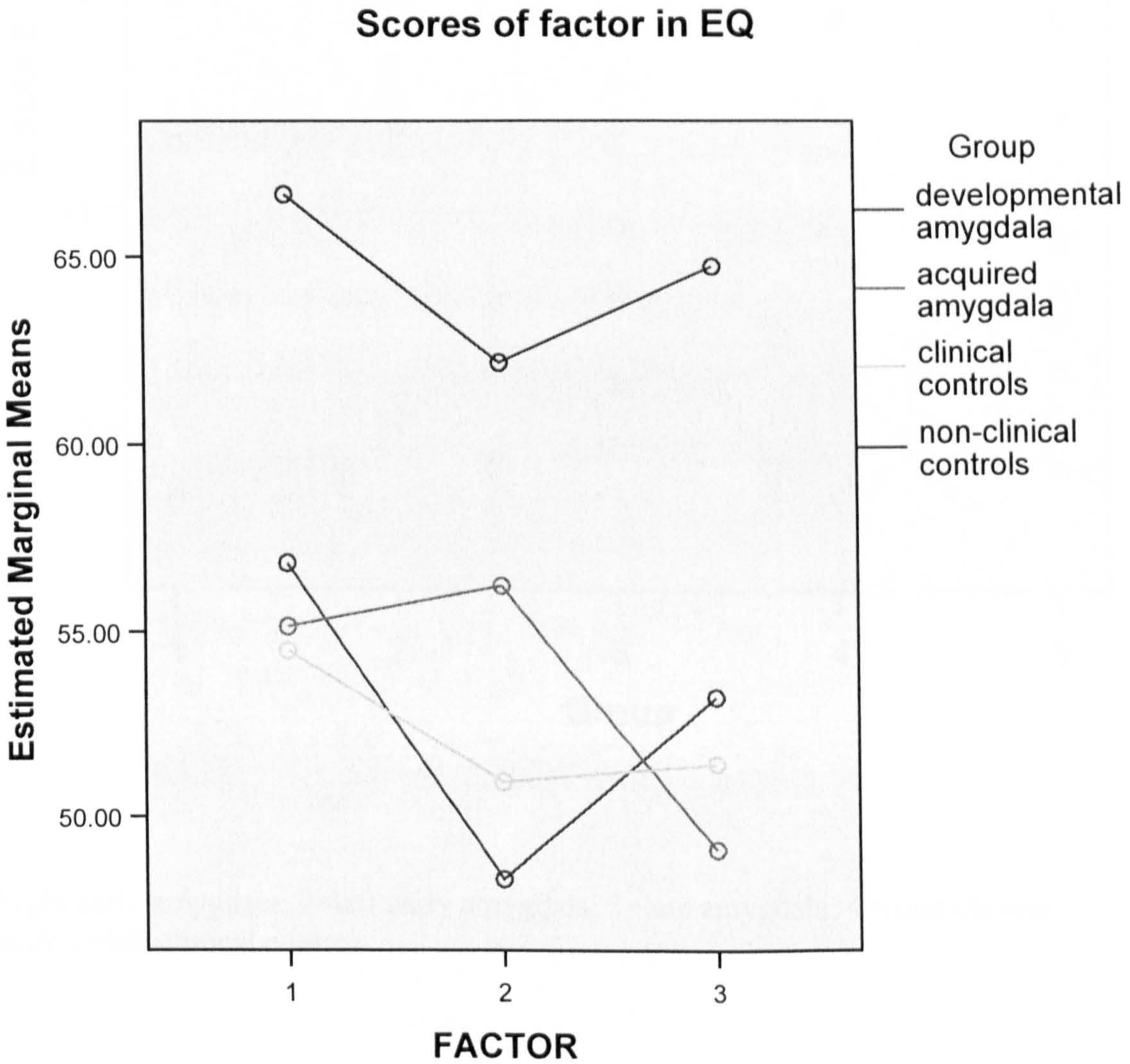
The three factors of the EQ were entered as a within subjects factor and group as the between subjects factor in a repeated measures ANOVA (including a total of 28 of the original 40 items which loaded onto the factors). There was no main effect of factor ($F(2,180)=0.93$, $p=0.4$) and no significant interaction of factor and group ($F(6,180)=0.30$, $p=0.94$)- see Figure 7.1. There was a significant main effect of group ($F(3,90)=2.81$, $p=0.04$, but no significant pairwise group differences were found in post hoc analyses with Bonferroni correction.

7.5.3 Laterality

We tested for laterality effects, dividing the early amygdala damage and clinical control groups by side. There was a significant overall group difference in total scores ($\chi^2=13$, $p=0.02$). No pairwise group comparisons survived adjustment for multiple comparisons. In unadjusted comparisons the right early amygdala damage and left clinical controls had significantly lower overall scores than healthy controls ($p=0.01$, Mann-Whitney), and the right early amygdala damage also scored lower than the right clinical controls ($p=0.05$). The pattern of results is illustrated below (figure 7.2). The total scores have been converted to Z scores based on the mean (62%) and SD (17%) of the healthy controls. There was no significant group difference in factor 1 ($\chi^2=7.8$, $p=0.17$) or factor 2 ($\chi^2=7.5$, $p=0.18$), but there was in factor 3 ($\chi^2=12.6$,

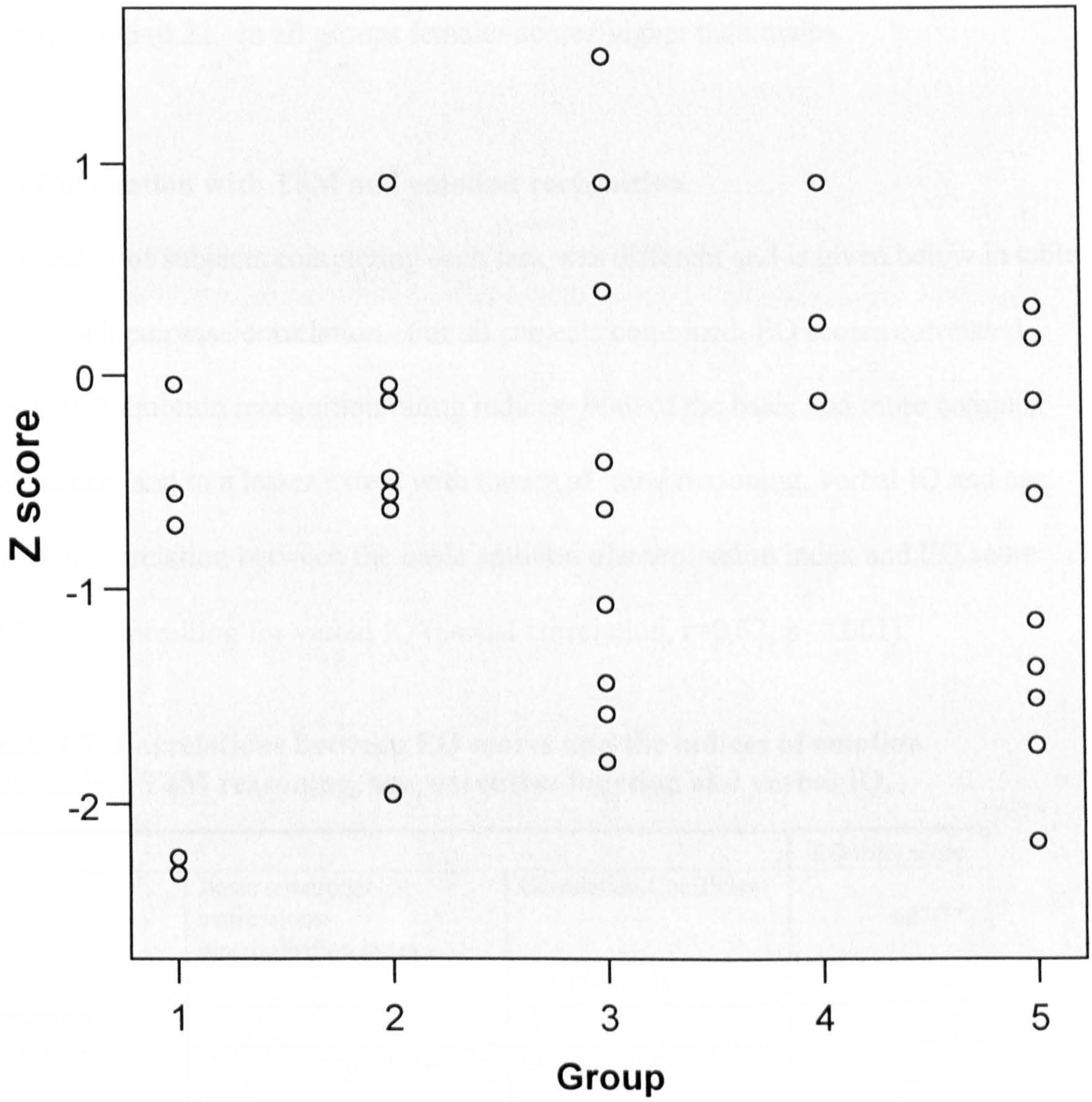
p=0.03). The late amygdala damage group scored less on factor 3 ('social skills') than both the healthy controls (p=0.01) and the right clinical controls (p=0.01). Additionally, the left clinical control scored less than healthy controls (p=0.01) and right clinical controls (p=0.01). None of these pairwise differences survived adjustment for multiple comparisons (at p<0.05).

Figure 7.1 Scores in the three factors of the EQ



Factor 1=cognitive empathy; Factor 2=emotional reactivity; Factor 3 =social skills.

Figure 7.2 Total scores in the EQ, expressed as number of standard deviations from the mean of the healthy controls.



1=Right early amygdala; 2=left early amygdala; 3=late amygdala; 4=right clinical control; 5=left clinical control.

7.5.4 Gender

Total EQ scores were entered as the dependent variable with group (early amygdala, late amygdala, clinical and healthy controls) and gender as fixed factors. There was a

main effect for gender (F(1,86)=11.8, p=0.001) with females scoring higher (mean 65% SD 15%) than males (mean 49% SD17%). There was no main effect for group (F(3,86)=2.1, p=0.10) and no significant interaction between gender and group F(3,86)-1.5, p=0.22. In all groups females scores higher than males.

7.5.5 Correlation with ToM and emotion recognition.

The number of subjects completing each task was different and is given below in table 7.7 for each pairwise correlation. For all subjects combined, EQ scores correlated highly with emotion recognition/rating indices- both of the basic and more complex expressions, and to a lesser extent with theory of mind reasoning, verbal IQ and age. The high correlation between the basic emotion discrimination index and EQ score held after controlling for verbal IQ (partial correlation, r=0.62, p<0.001).

Table 7.7 Correlations between EQ scores and the indices of emotion recognition, ToM reasoning, age, executive function and verbal IQ.

			EQ total score
Spearman correlations	Basic emotional expressions- discrimination index	Correlation Coefficient	.687(**)
		Sig. (2-tailed)	.000
		N	39
	Complex expressions- total score	Correlation Coefficient	.449(**)
		Sig. (2-tailed)	.002
		N	45
	Theory of mind reasoning	Correlation Coefficient	.240
		Sig. (2-tailed)	.112
		N	45
	Age	Correlation Coefficient	.205
		Sig. (2-tailed)	.177
		N	45
	Verbal IQ	Correlation Coefficient	.239
		Sig. (2-tailed)	.113
		N	45
	Hayling task	Correlation Coefficient	.131
		Sig. (2-tailed)	.402
		N	43

Correlations within each group are given below, and demonstrate the highly significant correlation between the measures of basic emotional expression recognition and EQ scores in all groups- most strikingly in the early amygdala damage group.

Table 7.8 Correlations between EQ scores and emotion recognition, ToM reasoning, age, Haylings test, and IQ for each group.

		Early amygdala	Late amygdala	Clinical controls	Healthy controls
Basic emotional expressions-discrimination index	Spearmans Correlation Coefficient	0.92	0.40	0.73	0.50
	Sig. (2-tailed)	<0.001**	0.60	0.02*	0.05*
	N	10	4	9	16
Complex expressions-total score	Correlation Coefficient	0.15	-0.08	0.35	0.45
	Sig. (2-tailed)	0.66	0.84	0.32	0.08
	N	11	8	10	16
Theory of mind reasoning	Correlation Coefficient	-0.03	0.40	0.09	-0.22
	Sig. (2-tailed)	0.94	0.32	0.80	0.42
	N	11	8	10	16
Age	Correlation Coefficient	-0.10	0.30	0.47	0.38
	Sig. (2-tailed)	0.77	0.47	0.17	0.14
	N	11	8	10	16
Verbal IQ	Correlation Coefficient	0.00	-0.17	0.09	-0.04
	Sig. (2-tailed)	1.00	0.69	0.80	0.89
	N	11	8	10	16
Hayling task	Correlation Coefficient	0.34	0.39	-0.07	-0.20
	Sig. (2-tailed)	0.34	0.39	0.85	0.45
	N	10	7	10	16

7.6 Conclusions

Across all participants the recognition of basic and complex expressions correlated modestly. Recognition of the complex, but not basic emotional expressions correlated significantly with an index of theory of mind abilities. This supports the concept of the 'Eyes' task as involving a preliminary stage of a theory of mind inference- that is inferring the general category of mental state of another person- for example detecting that someone is worried about something (Baron-Cohen, Wheelwright et al. 2001). It is noteworthy that the two tasks which showed sensitivity to the stage of amygdala damage, namely the theory of mind and emotional memory tasks, were also highly correlated. Within each group, correlations were very modest in part reflecting the small sample sizes.

Contrary to expectations there was no significant group difference in self-rated empathy scores. Thus, there was no evidence that early amygdala lesions were associated with lower self rated empathy. The EQ scores correlated highly in all groups with tasks of emotion recognition, particularly in the ability to discriminate between the basic emotional expressions. Correlations with measures of theory of mind reasoning were positive, but modest and not significant.

The lack of association between lesions of the amygdala and lower self rated empathy was unexpected, particularly in view of poor theory of mind reasoning in the early amygdala damage group. It weakens models claiming that early damage of the amygdala disrupts processing of affective stimuli, leading to aberrant early experience in social communication and development of abnormal empathy.

There are several important considerations which might modify this conclusion. Firstly, self-report measures are of necessity dependent on the degree of insight a person has into their skills and abilities. If a person truly lacks empathy, would they be aware of these deficits? However, the ability of scales such as the EQ to separate people with Asperger's syndrome (which has a lack of empathy as a core feature) from healthy controls suggests that self-ratings of empathic skills may indeed be valid. A second feature of the EQ is the breadth of skills and attributes it assesses. There are not only aspects indicative of cognitive empathy, but also measures of the tendency to react in an emotional manner to others, and assessment of self-perceived skills in social settings. However, the main deficits found in the amygdala damage group were in the social skills component, which appear less intimately related to theory of mind reasoning skills than the factor reflecting cognitive empathy. A final consideration is that the amygdala is only one of a myriad of structures likely to be necessary for the development of empathy, and thus the effects of its damage are likely to be small and may be missed by our study. However, the amygdala theory of empathy and indeed autism implies the structure is necessary for the development of the social cognitive skills(Baron-Cohen 2004). Thus we would expect large effects, which should be detected in a relatively homogenous group of subjects with relatively focal amygdala lesions.

EQ scores correlated strongly and consistently with emotion recognition, particularly the ability to discriminate the basic emotions, whereas correlations with theory of mind reasoning were modest. This pattern of results was unexpected; theory of mind skills would appear to be more proximately related to empathic skills than the more

basic processes of emotion recognition. In their study of patients with prefrontal lobe damage, Shamay-Tsoory and colleagues indeed reported this pattern of findings, with no correlation between emotion recognition and self-reported empathy, but a high correlation between theory of mind reasoning skills and empathy(Shamay-Tsoory, Tomer et al. 2003; Shamay-Tsoory, Tomer et al. 2005). It is possible however that the accurate interpretation and recognition of simple affective states serves as the foundation for the development of the detection of more complex affective and epistemic states and the subsequent ability to introspect about these skills. This contention is supported by the correlation between EQ and emotion recognition skills in the healthy controls suggesting that the results may reflect a normal developmental sequence. In the early amygdala damage group the extremely high correlation between emotion recognition and EQ scores suggests that the loss of the most basic emotional recognition abilities may have more deleterious effects on empathic skills than deficits in the more developmentally recent theory of mind skills. By contrast, the late amygdala damage group, showed no such correlation suggesting that the early (presumed) intact ability to process the basic emotional expressions scaffolds the development of more complex skills. The correlations with IQ were modest and generally non-significant and suggest that the results are unlikely to reflect merely group differences in IQ.

In future work it may be worthwhile to explore the ratings of empathic skills given to subjects with amygdala lesions by others, which might show a discrepancy between the self and other perception of empathic skill.

Inferring developmental processes from such cross sectional data in adults only is fraught with difficulties. Theoretically more informative approaches include cross sectional studies on subjects at different developmental stages, perhaps including children and adolescents with amygdala lesions. Longitudinal studies are the most powerful way to chart development, but are not practicable in subjects with rare lesions. However, the author is currently analyzing data from the National Institute of Mental Health cohort of typically developing children who had repeated neuroanatomic magnetic resonance imaging combined with an assessment of some aspects of social cognitive skills. This allows us to chart the changing neural substrate that accompanies social cognitive development.

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Chapter 8. A prospective study of the effects of anterior temporal lobectomy for treatment of epilepsy on social cognition.

8.1 Summary

Twenty-one participants undergoing anterior temporal lobectomy for treatment of medically intractable epilepsy were tested pre and post operatively on tests of emotional recognition and theory of mind reasoning. There were no significant differences between these operative groups and healthy controls in the change in performance on a battery of tests of theory of mind reasoning and the recognition of complex emotional expressions. However, following a left anterior temporal lobectomy, there was an improvement in the ability to rate frightened facial expressions as being fearful We interpret the finding as reflecting an improvement in metabolic and neurophysiological function of the right amygdala following the excision of a noxious inhibitory ictal focus on the left. We demonstrated earlier that damage to the right amygdala is associated with impaired processing of fear; amelioration of right amygdala function is conversely associated with an improvement its recognition.

8.2 Introduction.

The majority of neuropsychological studies examine people who have sustained 'static' focal lesions at one time point only, inferring from the pattern of deficits associated with the lesion the function of the structure in normal processing. Few studies of social cognition have explored prospectively, the effects of excision of a lesion on function.

Subjects with lesions of the amygdala and/or surrounding anterior temporal lobe structures frequently have epilepsy associated with the lesion. A proportion of the people have epilepsy which proves resistant to medical treatment and progress to operative excision of the lesion, typically as part of an anterior temporal lobectomy. Such subjects provide an opportunity to study the cognitive effects of removal of a 'noxious' (epileptogenic) lesion. Such a prospective design is particularly powerful, as it allows within subjects comparisons to be made, and partly controls for between subjects variance, reducing error. There are three possible outcomes of the excision of the lesion:-

1) A deterioration of function which could be interpreted as the effects of moving from a partial to complete lesion of the amygdala and/or surrounding anterior temporal lobe structures. Most patients with intractable mesial temporal lobe epilepsy have pre-operative mesial temporal sclerosis which usually affects the amygdala with variable degrees of neuronal loss (Yilmazer-Hanke, Wolf et al. 2000). Thus pre-operatively the patients effectively have a partial amygdala lesion. Standard en bloc resection of the anterior temporal lobe results in the complete excision of the amygdala in this group, leading to a complete amygdala lesion. Thus a deterioration of function following an ATL could be viewed as the result of a progressive lesion.
2) No change in function would be expected if the diseased or damaged amygdala/anterior temporal lobe played no role in the performance of a function.
3) Improvement in function is the final option. A recent case study reported an improvement in the ability to discriminate frightened facial expressions from the

other basic emotions in a patient who underwent a left anterior temporal lobectomy (Yamada, Murai et al. 2005). The authors attributes the improvement to the excision of a 'hyperexcitable' amygdala which pre-operatively led to the misinterpretation of facial emotional stimuli as depicting high degrees of fear, sadness or anger - even in faces in which healthy subjects do not see these blends of negative emotions. Excision of this dysfunctional amygdala thus corrected this interpretative bias and thus ameliorated the recognition of emotional expressions.

Another model emphasizes the dynamic effects that functionally active lesions can have on interconnected structures, often inhibiting them. Particularly rich information can be gleaned from patterns of recovery when such lesions are excised. An epileptogenic focus in the amygdala/anterior temporal lobe is the ideal model of such a lesion: there is extensive evidence from PET and MRS studies that an epileptogenic focus in the mesial temporal lobe (typically arising from a sclerotic lesion) is associated with hypometabolism of temporal, inferior frontal and thalamic regions, both ipsilaterally and contralaterally(Chassoux, Semah et al. 2004). Strong interhemispheric connections between lesions in the anterior temporal lobe and their contralateral homologue have also been demonstrated anatomically and neurophysiologically. (McIntyre and Poulter 2001; Wilder 2001; Khalilov, Holmes et al. 2003). After excision of the ictal focus there is a reversal of many of these abnormalities with ipsilateral and contralateral normalisation of metabolism(Hugg, Kuzniecky et al. 1996; Cendes, Andermann et al. 1997; Vermathen, Ende et al. 2002). Such normalisation would

be expected to have behavioural consequences. Deficits in executive functions thought to be mediated primarily by frontal cortical regions have been demonstrated in subjects with mesial temporal lobe sclerosis and attributed to the dynamic inhibition of frontal function(Hermann, Seidenberg et al. 1991). After surgery, there is often evidence of 'release of function' with improvement in some executive cognition measures(Hermann and Seidenberg 1995; Martin, Sawrie et al. 2000; Martin, Sawrie et al. 2000). In one study, 58% of subjects with impaired executive function moved from abnormal to normal range performance after excision of an ictal focus(Hermann and Seidenberg 1995).

We used a similar pre and post-operative design to explore the possibility that an epileptogenic lesion in the temporal lobe can actively inhibit aspects of social cognition through its possible metabolic and neurophysiological inhibitory effects on other components of the circuit, such as the contralateral amygdala. Such inhibition would be reflected in an improvement in social cognitive skills after the excision of the noxious lesion. The findings from this approach can complement inferences based on the more classic neuropsychological approach which usually study subjects with chronic focal lesions. For example, if subjects with a chronic stable lesion of the comprising right amygdala have a selective deficit in the detection of certain emotional expressions, this implicates the right amygdala in the detection of these basic emotions. Following a left ATL we postulate that there may be an improvement in the function of interconnected structures such as the right amygdala. This could results in an improvement in the

processing of the same group of emotions, corroborating the role of the right amygdala in the processing these emotions.

We thus compared the ability to recognize and reason about the mental states of others on subjects with medically intractable epilepsy arising from a lesion in the mesial temporal lobe. Subjects were tested while the epileptogenic lesion was still active and after its excision, which in all cases was associated with either a cessation of marked reduction in seizure activity. Experimental designs measuring change in performance in tasks over time are prone to artifacts arising from factors such as practice effects, regression to the mean and lack of reliability in the tasks. We thus included a comparison group of healthy control subjects who were also tested on two occasions. It is also important to exclude a general non-specific improvement in cognitive functioning following improved well-being following successful treatment of chronic epilepsy. Hence we were interested in showing specific improvements on key tasks over an above any generalized gains. There were no a prior hypotheses in this exploratory study.

8.3 Methods

8.3.1 Participants.

All clinical subjects were recruited from the Surgical Epilepsy Programme at the Regional Neuroscience Centre at King's College London.

1) Anterior temporal lobectomy group (ATL). Twenty subjects were tested between 1-3 months pre-operatively and 4-6 months post-operatively. All subjects had an

en bloc ATL resection, extending on average 3.5cm from the temporal pole on the left and 4.5 cm on the right, incorporating the entire amygdala and anterior portions of the hippocampus. No subjects had any alterations of their anticonvulsant medications in the post-operative period (with reduction in medication typically starting at the one year review). Post-operatively all subjects included were either completely seizure free or had a substantial improvement in their seizures.

2) Twenty one healthy comparison subjects with no history of neurological or psychiatric history were tested twince at a 3-9 month interval (mean 6months).

8.3.2 Tasks

Standard neuropsychometry.

To determine IQ, the clinical groups completed subtests of the Wechsler Adult Intelligence Scale-III (for verbal IQ the vocabulary, digit span, comprehension and similarities subscales, for performance IQ the block design and object assembly subscales.) For the neurologically intact control subjects an estimate of IQ was obtained from the National Adult Reading Test(Nelson 1982). All clinical subjects also completed The Benton Facial Recognition task which requires the matching of faces of identical individuals taken under different levels of illumination and at different angles (Benton, Sivan et al. 1983).

Experimental tasks. Ekman and Friesen series of pictures of facial affect were used in the experimental task (Ekman and Friesen 1976).

Labeling task. Six faces portraying each of six basic emotions plus the neutral facial expression were presented in randomized order and subjects were asked to choose which one of the six basic emotional terms best matched the facial expression.

Intensity rating task. Four of the six identities (two male and two female) portraying all six of the basic emotions were then presented. As each of the 24 faces was presented subjects were asked to rate the intensity of one of the six basic emotion terms (sad, happy, surprise, anger, fear, disgust). The rating scale was presented below the face and ranged from 1 (not at all) to 10 (very much). After rating all faces on this emotional term, the faces were again presented and the subjects asked to rate the intensity of the face with respect to a new emotional term. Thus in total the subjects were presented with each of the 24 faces on six occasions. The ratings given for each face to its 'correct' label (the rating for the emotional label 'sad' given in response to each sad face) was defined as the congruent rating. The mean of all the ratings given in response to the same face for the 'incorrect' labels (i.e. for a sad face, the mean of the responses given to the labels 'happy/frightened, surprised etc') was taken as the incongruent rating. A discrimination index was calculated as the difference between the congruent and incongruent ratings. A high discrimination index means that the individual sees a face as its prototype rather than resembling the other basic emotions (thus the 'sad' face is not seen as containing nuances of happy, angry, fearful expressions). A low discrimination

index implies that the individual sees, for example, the prototypically sad face as being less distinctly 'sad' and resembles happy, sad, angry, fearful and surprised expressions.

8.4 Results

8.4.1 Demographic and clinical details.

Subjects did not differ in age at testing ($F(2,38)=2.14$, $p=0.13$). Both operative groups had a significantly lower IQs than the healthy controls (for verbal IQ:$F(2,38)=5.1$, $p=0.01$; performance IQ $F(2,38)=6.9$, $p=0.003$; pairwise contrast with healthy controls, for VIQ RATL<NV; for PIQ RATL, LATL<NV, all $p<0.05$, corrected). The right and left ATL groups did not differ significantly in gender ($\chi^2=1.5$, $p=0.48$), handedness (Fisher's exact test $p=0.58$) or duration of epilepsy ($t(18)=0.57$, $p=0.57$), but did have a significantly younger age of onset of habitual seizures ($t(18)=2.4$, $p=0.03$).

Table 8.1 Demographic and clinical characteristics of participants (means (SD).

	M:F	Age, years	Handedeness (predominately R handed)	VIQ	PIQ	Pathology MTS:focal:none	Onset of epilepsy, age in years	Duration of epilepsy, years
R ATL	5:5	41 (9)	9	97 (18)	98 (20)	6:2:2	18 (11)	22 (11)
L ATL	3:7	33 (11)	8	103 (17)	98 (12)	6:4:0	8 (8)	26 (14)
Healthy controls	6:15	33 (11)	18	112* (6)	112* (4)	-		

*Estimated from the NART. MTS=mesial temporal sclerosis

8.4.2 Emotion intensity rating.

The intensity rating task was completed by 19 ATL and 19 healthy control subjects. Two subjects in the healthy control and one in the ATL group failed to complete the repeat full testing and so are not included. Mean ratings for the congruent ('fear' rating for a frightened face) and for the incongruent ratings (average of 'sad', 'happy', 'digust', 'surprise' and 'happy' to a frightened face) are shown in table 8.2. Scores are given for each group at time 1 (pre-operatively for the clinical group) and time 2 (post-operatively for the clinical groups).

A discrimination index (congruent-incongruent rating) was calculated and used as the dependent variable in a repeated measures ANOVA with stage of testing (pre/post-op) as a within subjects factor and group (R ATL, LATL and healthy controls) as the between subjects factor. Separate analyses were conducted for the discrimination index for all six emotional categories combined, and for each emotional category separately Table 8.3.

Table 8.2 Mean (and standard deviations) congruent and incongruent ratings for each emotion.

	R ATL				LATL				Healthy controls			
	Pre-op		Post-op		Pre-op		Post-op		Pre-op		Post-op	
	M	SD	M	SD	M	SD	M	SD	Mean	SD	M	SD
All emotions-congruent rating	7.59	2.01	7.65	1.76	8.34	0.80	8.26	0.78	8.11	1.08	8.22	0.90
All emotions-incongruent rating	3.39	1.18	3.23	1.03	3.41	1.15	3.01	0.85	2.19	0.67	2.02	0.71
Anger-congruent	8.11	2.33	8.20	1.87	8.86	0.81	8.44	1.47	8.43	1.34	8.33	1.22
Anger-incongruent	3.87	1.42	3.21	1.30	3.64	1.56	3.57	0.97	2.30	0.92	2.16	0.98
Disgust-congruent	7.19	1.95	7.25	2.06	8.00	0.93	8.34	1.61	8.24	1.45	8.14	1.41
Disgust-incongruent	3.53	1.31	3.35	0.87	3.52	1.23	3.18	1.11	2.33	0.81	2.16	0.95
Fear-congruent	7.70	2.32	7.05	1.95	8.36	2.07	8.23	0.90	7.86	1.07	7.72	1.23
Fear-incongruent	4.22	1.65	3.86	1.31	4.68	1.57	2.87	0.91	2.87	0.73	2.74	0.93
Happy-congruent	8.76	1.70	9.13	1.09	9.69	0.48	9.39	0.80	8.51	1.40	8.71	1.11
Happy-incongruent	1.73	0.70	1.82	0.75	1.47	0.61	1.71	0.57	1.17	0.21	1.10	0.19
Sad-congruent	6.12	2.75	6.73	2.60	7.22	1.55	7.51	1.55	7.70	1.20	8.13	1.28
Sad-incongruent	3.32	1.15	3.41	1.16	3.36	1.22	3.28	0.97	2.13	0.96	1.84	0.90
Surprise-congruent	7.66	2.55	7.55	2.71	7.92	1.33	7.43	1.54	7.91	1.58	8.26	1.42
Surprise-incongruent	3.69	1.62	3.73	1.51	3.77	1.59	3.43	1.25	2.36	0.75	2.09	0.77

Table 8.3 Discrimination index for all emotional categories for each group

	Group	M	SD	N
Pre-op	RATL	4.20	2.09	10
	LATL	4.92	1.11	9
	NV	5.92	1.06	19
Post-op	RATL	4.45	1.71	10
	LATL	5.21	1.12	9
	NV	6.20	.90	19

There was a trend for general improvement across all subjects moving from time 1 to time 2 testing (pre versus post $F(1,35)=3.3$, $p=0.08$). In the discrimination index for all emotional categories combined, there was a main effect for group ($F(2,35)=6.8$, $p=0.003$), with the RATL having a significantly lower index than the healthy controls ($p=0.003$, corrected).

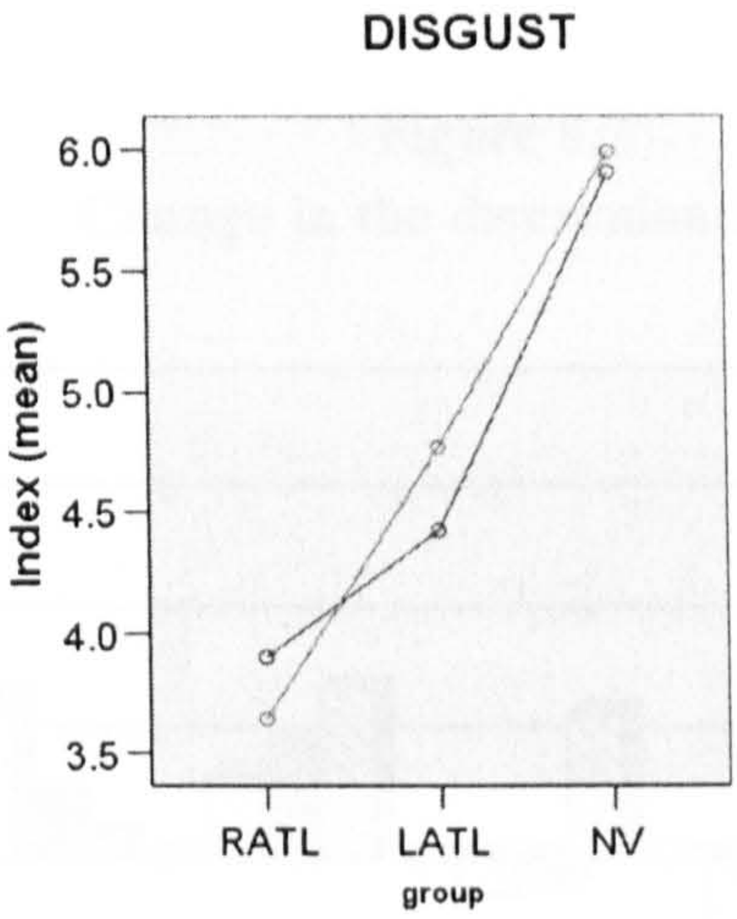
Within individual emotional categories, a significantly lower discrimination index in the R ATL relative to healthy controls was found for disgust ($p=0.002$), sad ($p<0.001$), surprise ($p=0.02$) and fear ($p=0.02$). The LATL group had a significantly lower discrimination index relative to healthy controls for sad ($p=0.002$) and surprise ($p=0.05$).

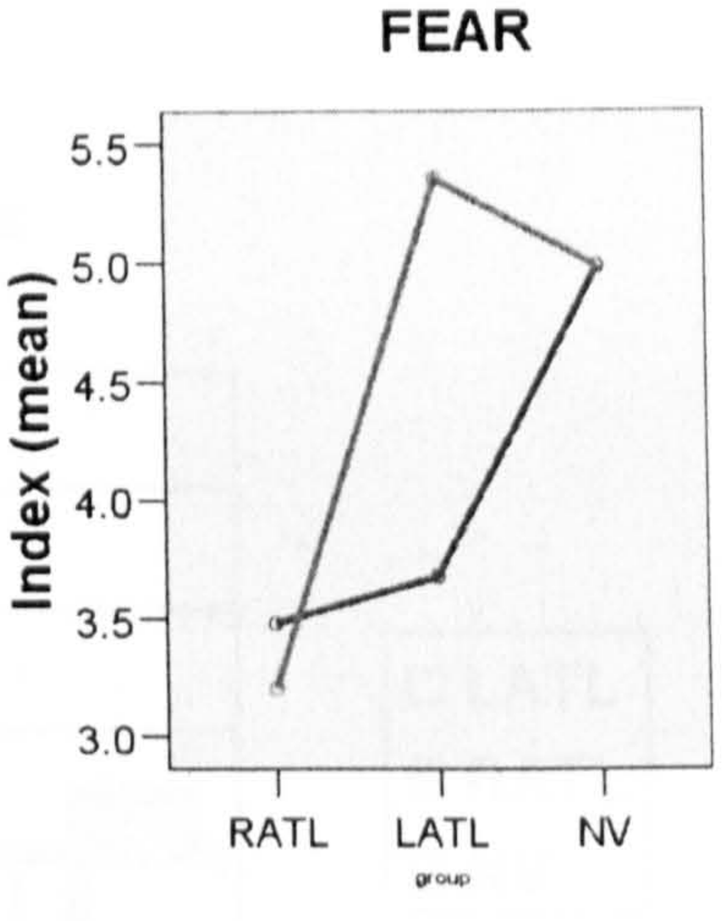
To examine whether the left and right ATL groups behaved differently as a result of the operation, we examined for significant interactions between stage (pre vs post-op) and group. There was no significant interaction for mean overall ratings ($F(2,35)=0.02$, $p=0.98$). There was a similar lack of significant interactions for anger ($F(2,35)=2.1$, $p=0.14$), disgust ($F(2,35)=0.26$, $p=0.77$), happiness ($F(2,35)=1.9$, $p=0.16$), sad ($F(2,35)=0.16$, $p=0.85$) and surprise ($F(2,35)=0.98$, $p=0.38$). However, in the ratings of

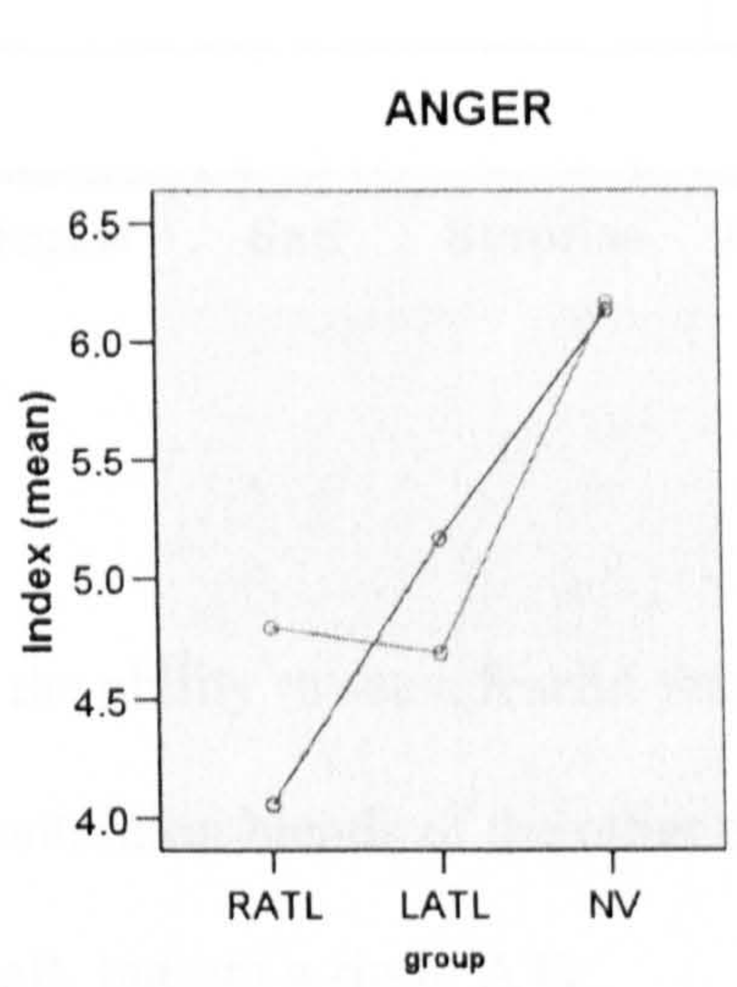
fear there was a near significant interaction F(2,35)=3.04, p=0.06). The pattern of results is shown for each emotion below- Figure 8.1.

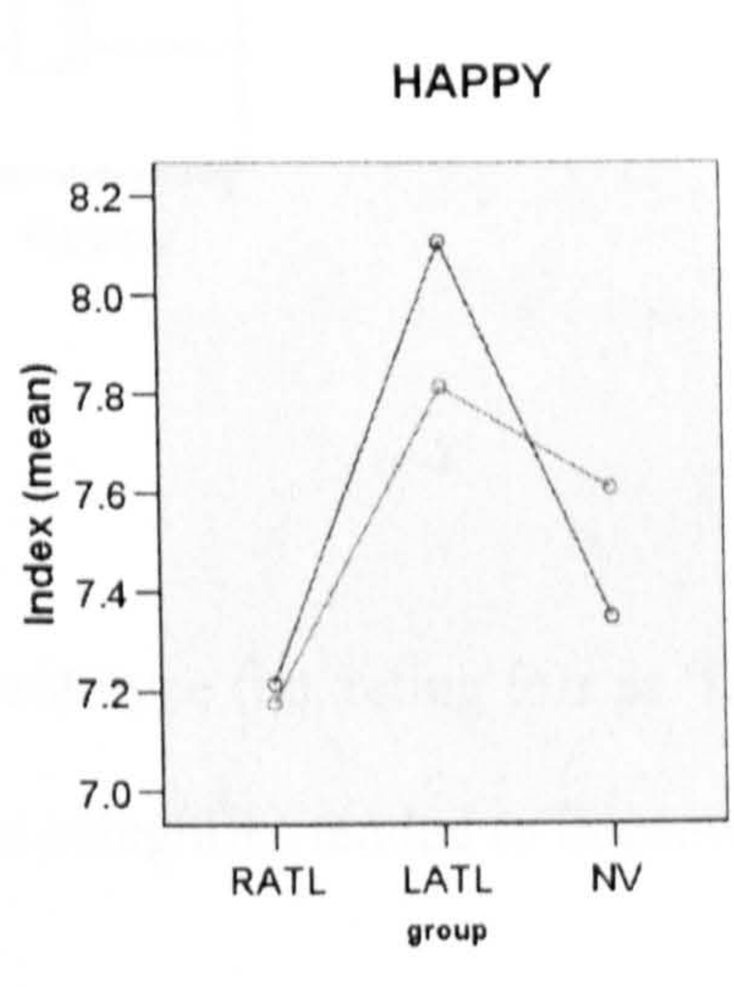
To explore the near significant interaction between stage of testing and group for fear expressions, we conducted one way ANOVAs at time 1 (pre-operative) and time 2 (post-operative). These showed a significant group difference post-operatively (F(2,35)=6.2, p=0.005), but not pre-operatively (F(2,35)=2.9, p=0.07). Post-operatively the RATL group had a significantly smaller discrimination index than the LATL (p=0.009) and the healthy controls (p=0.01). This further illustrated in Figure 8.2 below, which shows the change in the discrimination indices for fear, compared with the ratings for all six emotional categories. A positive value indicates an improved ability to rate an emotion as its prototype.

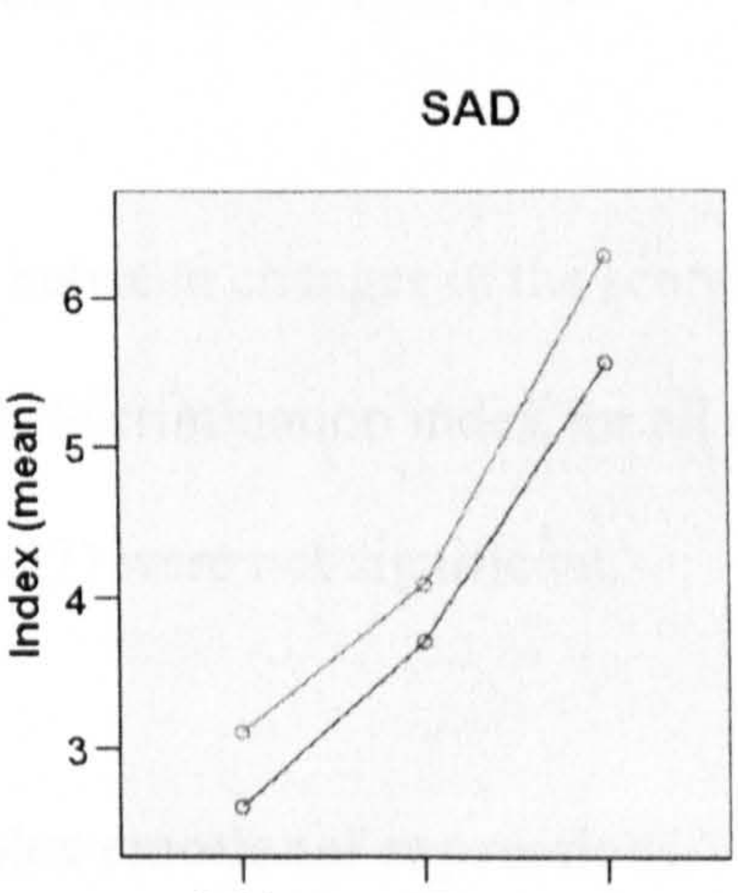
Figure 8.1 Change in discrimination index for each emotion.

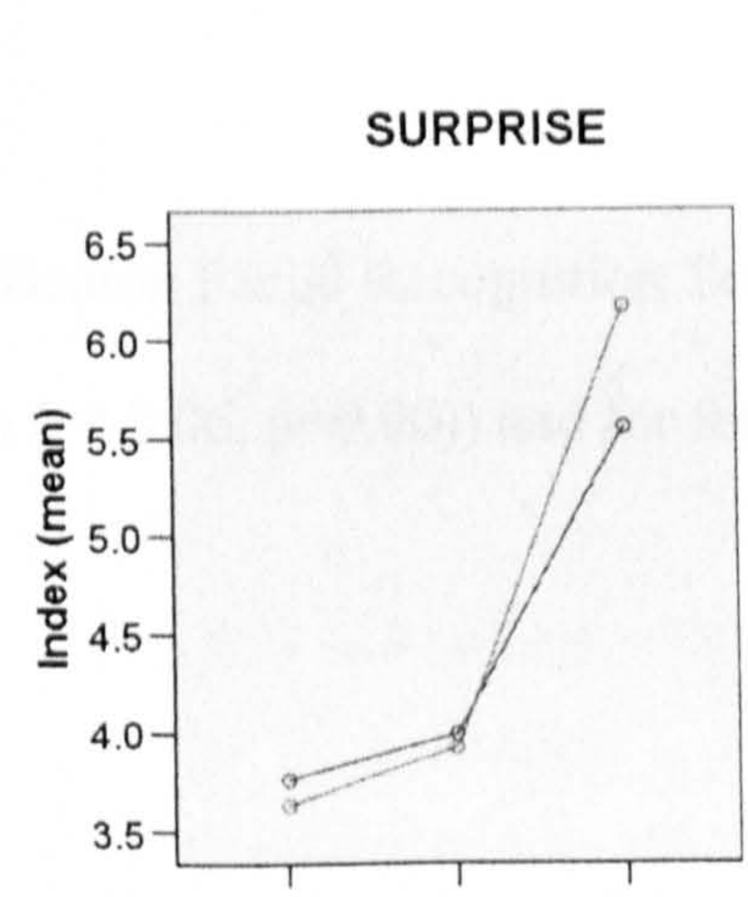








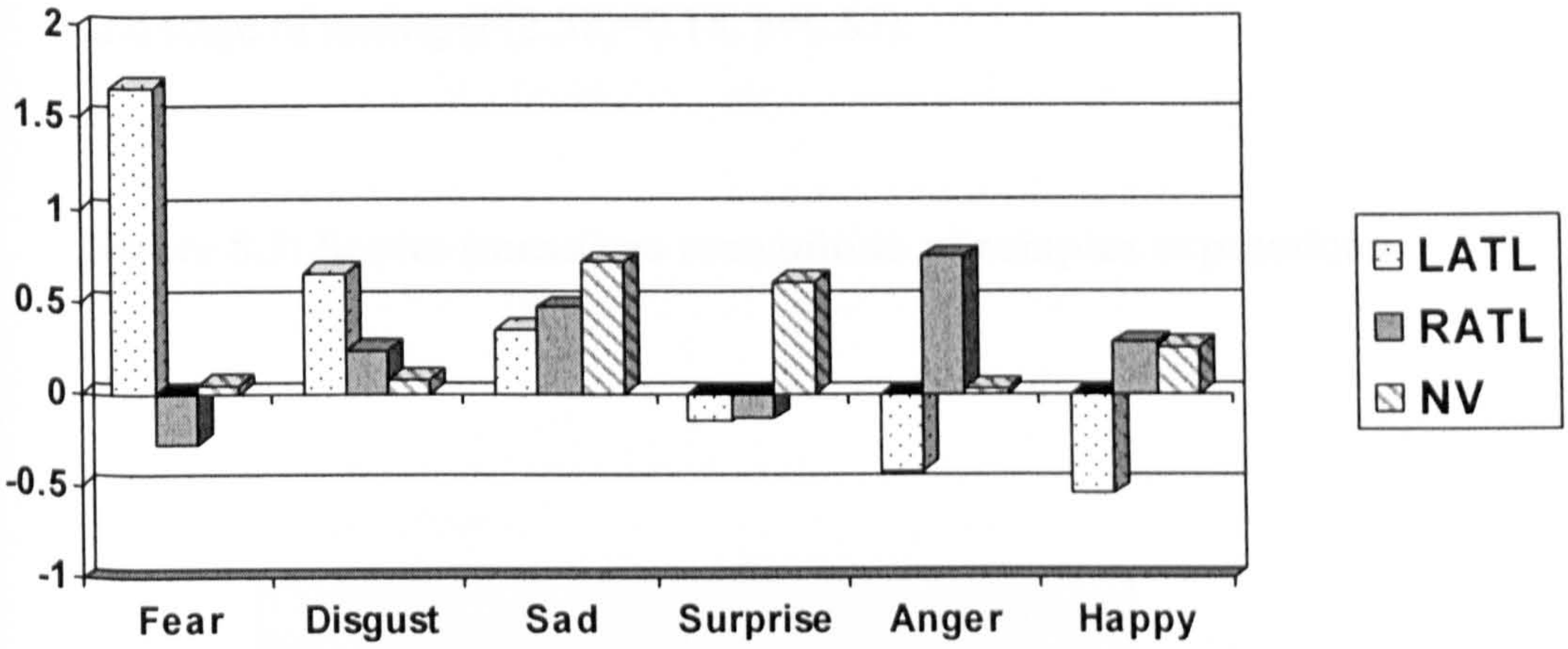




—— =Pre-operative (time 1) —— =Post-operative (time 2)

Figure 8.2

Change in the discrimination index



In summary, the ability to see a fearful face as its prototype (i.e. rating fear as 'fear') rather than containing blends of the other emotional categories tended to improve following a left, but not a right, ATL.

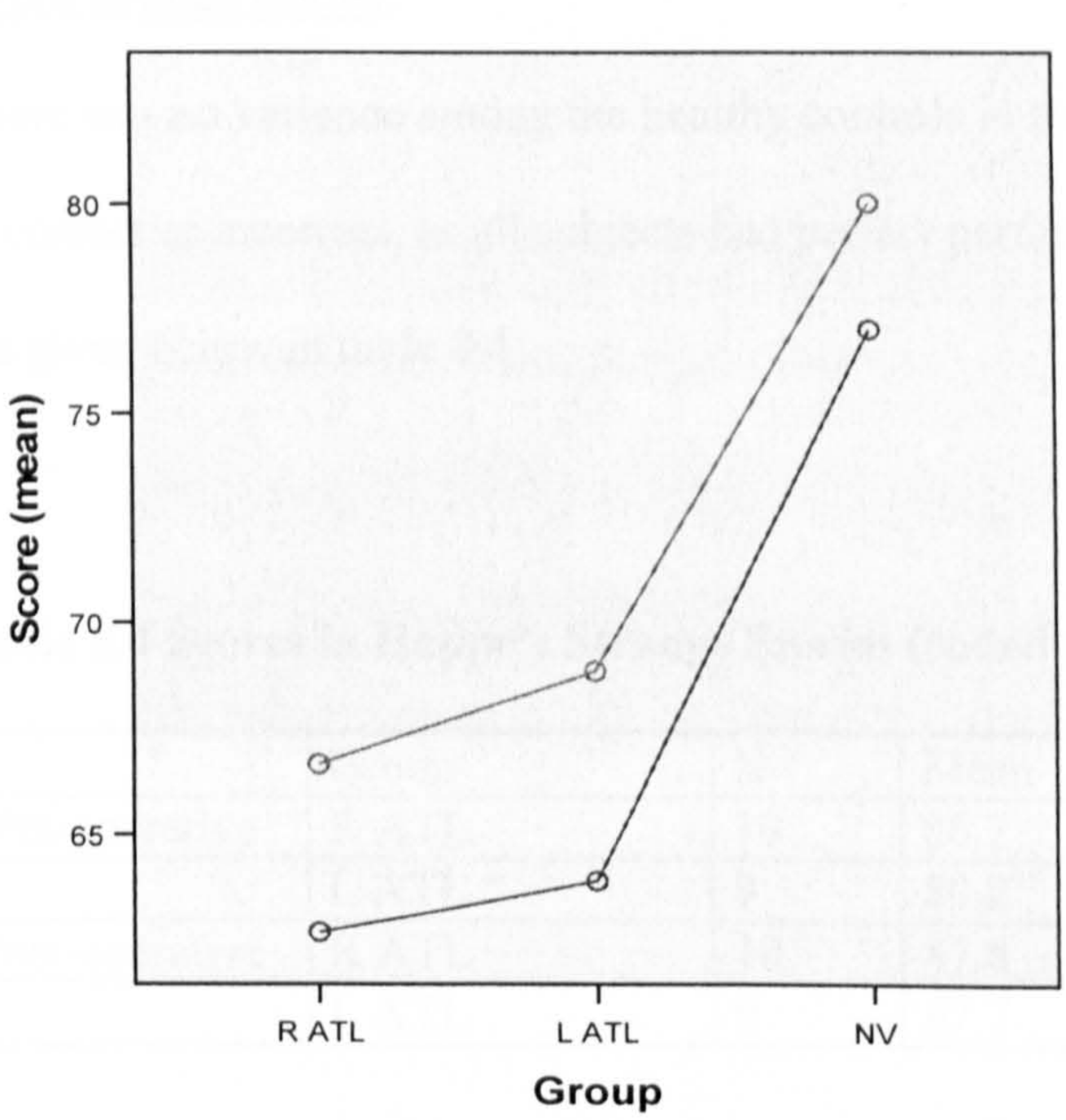
Correlations between changes in the scores on the Benton Facial Recognition Test and change in the discrimination index for all emotions ($r=-0.06$, $p=0.80$)) and for fear alone ($r=0.21$, $p=0.37$) were not significant.

8.4.3. Complex emotional expressions.

In a one way ANOVA, there was a significant group difference in overall scores $F(2,36)=11.6$, $p<0.001$, with both the right and left ATL groups being less accurate in

overall recognition than the healthy controls ($p<0.001$)- Figure 8.3. There was also an effect of stage of testing with an overall improvement on second testing ($F(1,36)=8.2$, $p=0.007$) (mean score on pre-operative/time 1 testing 71% (SD12.1%) and post-oeprative/time2 testing 74% (SD10.2%). There was no significant interaction of group and stage of testing ($F(2,38)=0.18$, $p=0.83$).

Figure 8.3: Scores (mean) on recognition of complex expressions



Key: R ATL= right anterior temporal lobectomy; L ATL= left anterior temporal lobectomy; NV= healthy controls

—— =Pre-operative (time 1)

—— =Post-operative (time 2)

8.4.4 Theory of mind reasoning.

<u>False belief tasks</u>.

No subjects in any group made any errors on the first order false belief task either pre or post operatively. At baseline, errors in second order false belief tasks were made by one subject in the RTL, two in the LTL and no healthy controls (χ^2=4.13, p=0.13). Post-operatively an additional subject in the RATL made an error (χ^2=4.6, p=0.10).

<u>Happe strange stories</u>.

There was no variance among the healthy controls in the scores in the task when marked as correct or incorrect, as all subjects had perfect performance. Scores of the ATL groups are given below in table 8.4.

Table 8.4 Scores in Happe's Strange Stories (coded as correct/incorrect)

	Group	N	Mean	SD
Pre-operative	R ATL	10	86.7	15.5
	L ATL	9	80.2	16.5
Post-operative	R ATL	10	87.8	12.2
	L ATL	9	87.7	11.7

However there was sufficient variance in scores to allow parametric analyses when the responses were coded scores according to the content of the response (full mental state, partial mental state or physical). Pre and post-operative scores on this measure were thus

entered in a repeated measures, with group as the between subjects variable- see table 8.5.

Table 8.5 Scores in Happe's Strange Stories coded according to content

	Group	N	M	SD
Happe- pre-operative	R ATL	10	78.9	17.1
	L ATL	9	68.5	21.9
	NV	21	85.2	12.1
Happe- post-operative	R ATL	10	80.0	14.6
	L ATL	9	78.4	15.8
	NV	21	87.3	11.3

There was a main effect of stage of testing, $F(1,37)=3.9$, $p=0.05$, with scores at second testing (mean 79.7, SD16.9) higher than those at first testing (mean 77.3, SD11.2). There was a significant group difference ($F(2,37)=3.2$, $p=0.05$), and pairwise post hoc comparisons there was a near significant impairment in the L ATL group relative to healthy controls (corrected $p=0.06$). There was no significant interaction $F(2,37)=2.7$, $p=0.26$.

Faux pas.

The total scores for the faux pas task were calculated as described earlier. For each group the data deviated substantially from normality and there was a significant difference in variance between groups. This was not improved by standard transformations, and thus non-parametric analyses were used. The median scores and quartiles for each group are given in table 8.6.

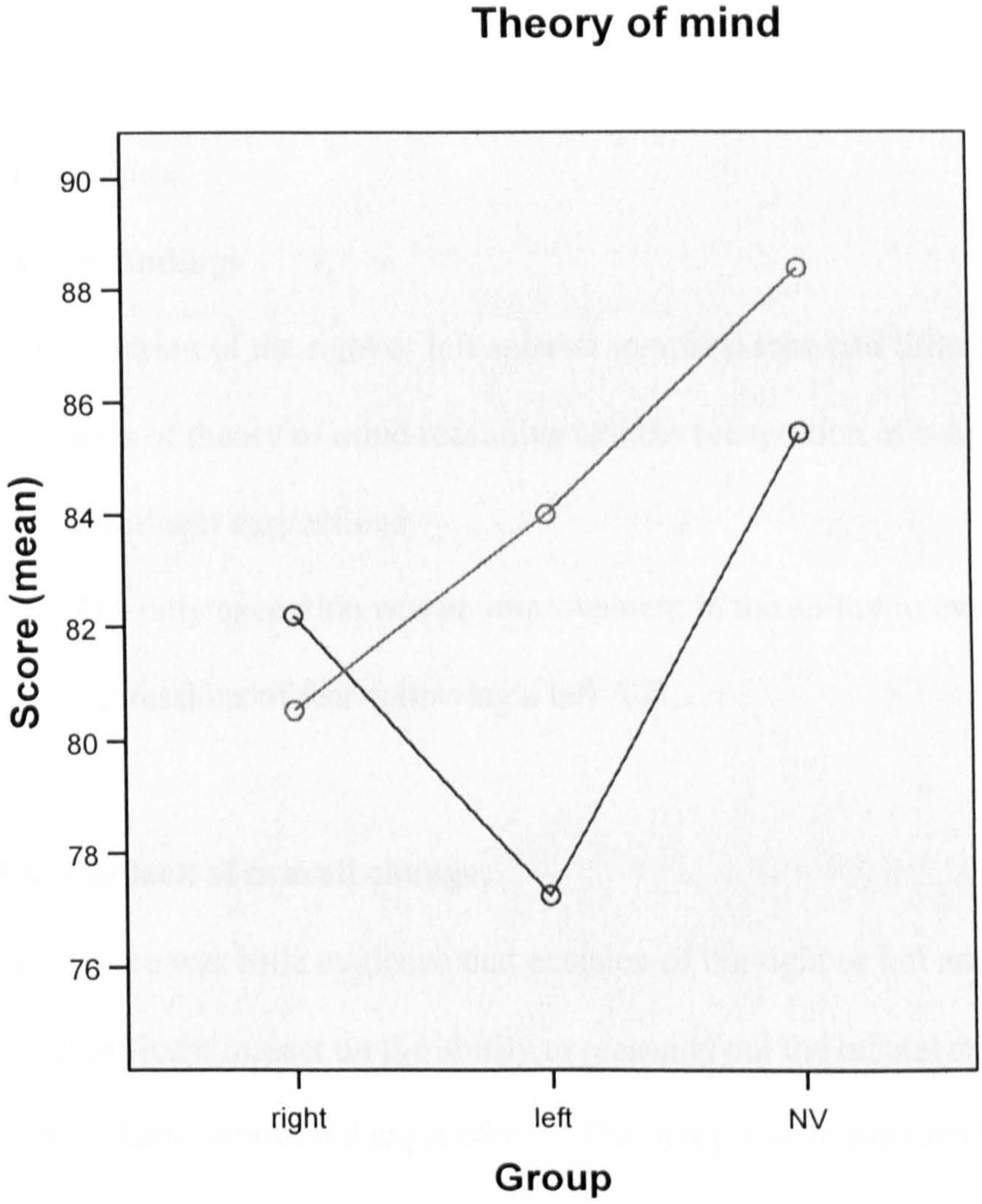
Table 8.6 Scores in faux pas task.

	R ATL	L ATL	NV
Pre-op	96 (78-100)	100 (87-100)	100 (73-100)
Post-op	94 (67-100)	100 (77-100)	100 (77-100)
Change score	-3.7 (-10.7 to 0.5)	0 (-7.4 to 0.2)	0 (0 to 6.25)

A change score for each group was calculated (post-op less pre-op scores) and is give above. A positive score indicates overall improvement. A Kruskal-Wallis test showed no significant group differences in this score (χ^2=4.1, p=0.13).

The total scores in the Happe Strange Stories and faux pas tasks were combined and expressed as a percentage. This score was used as the dependent variable in a repeated measures ANOVA with the stage of testing as the within subjects factor and group as the between subjects factor. There was no main effect of group (F(2,37)=1.0, p=0.37), or stage of testing (F91,37)=2.5, p=0.13) and no significant interaction (F(2,37)=1.7, p=0.2). This is illustrated in Figure 8.4.

Figure 8.4 Scores in theory of mind reasoning.



Key: right = right anterior temporal lobectomy; left=left anterior temporal lobectomy; NV=healthy controls.

—— =Pre-operative (time 1)
—— =Post-operative (time 2)

An important possible confounder of change in performance in ToM tests is alterations in executive function that can accompany an anterior TL. There was no correlation between the change in performance on the Brixton and Hayling's test and the change in scores in either Happe's Strange Stories (Spearman rho=-0.03, p=0.92) or the faux pas (rho=0.24, p=0.32).

8.5 Discussion.

8.5.1 Key findings

1) Excision of the right or left anterior temporal lobe had little effect on a battery of tests of theory of mind reasoning and the recognition of basic and complex emotional expressions.
2) The only exception was an improvement in the ability to evaluate facial expressions of fear following a left ATL.

8.5.2. The lack of overall change.

Overall there was little evidence that excision of the right or left anterior temporal lobe had a significant impact on the ability to reason about the mental states of others or the ability to detect emotional expressions. The first possible explanation is that the study had a small sample size and was thus only powered to detect small effects. A replication with a sample size informed by the results of this preliminary study, is needed.

The second possible explanation of the overall finding of little change in performance following ATL is that it indicates that the amygdala and surrounding structures are not

necessary for the detection of complex mental states and theory of mind reasoning. This explanation fits with our earlier findings of generally intact performance in ToM tasks among subjects who acquired complete lesions of the amygdala in adulthood through ATL. However we also reported that static amygdala lesions were associated with impairments in the recognition of complex facial expressions- an effect which was more marked for those with amygdala damage arising due to ATL in adulthood. This seems at odds with the minimal changes in complex expression recognition in the ATL groups- with both operative groups and the healthy controls all showing a slight overall improvement most consistent with a practice effect. It might suggest that the earlier findings are an artifact of differences between the early and late amygdala damage group which could have differentially affected the ability to recognize complex expressions (such between subjects differences are largely controlled in the prospective design used in this latter experiment). It is difficult to deduce which group differences might be important, as the results of the earlier experiment held after controlling for differences in intelligence, and the groups did not differ in gender, age or clinical variables such as medication history and duration of epilepsy. It is also possible that the 'Eyes' task is not sensitive enough to detect subtle changes that might be expected following the excision of just one structure in the network of brain regions that are recruited in a task which relies on engaging multiple cognitive domains.

8.5.3 Fear and the right amygdala.

Earlier we demonstrated that chronic lesions centering on the right amygdala are associated with abnormal processing of facial expressions of fear and sadness. This was

reflected in intensity ratings which suggest that the right amygdala is important in attaining perceptual clarity for these emotional categories, allowing each emotion to be seen as its prototype. Following a left temporal lobectomy which includes excision of the amygdala there was a near significant improvement in the ability to rate fear in a prototypical manner. This was a marked difference from the other emotional categories , which showed no significant group differences in the change in ratings. The pattern of findings is not explained by changes in more general face processing capabilities or indeed a general increase in well-being.

This pattern of results does not support the concept that an ATL results in a progressive lesion, moving from partial to complete amygdala damage, accompanied by a deterioration in function. Like the healthy controls, both operative groups showed little overall change in the discrimination index for all six emotional expressions, and a slight improvement.

This lack of change in emotional intensity ratings may mean that the amygdala/anterior temporal lobe are not necessary for emotion recognition. However, the bulk of the functional imaging and lesion literature support a pivotal role for the amygdala in emotion recognition. Additionally, the finding of no overall change in ATL groups was in mean ratings across all six emotional categories, and in the earlier study on patients with static lesions, we demonstrated specific impairments in the recognition of fear and sadness (and to a leser extent disgust) in those with right sided amygdala lesions. This emphasizes the need to look within each emotional category for changes in behaviour

that may accompany excision of an amygdala lesion. When the analyses are at this level, patterns of significant change are detected, arguing against the concept that the amygdala/anterior temporal lobes have no role in emotion recognition.

How can we adequately account for the differential *improvement* in discrimination ratings found for fear in the left ATL subjects. The model outlined earlier which invokes a 'release of function' of the right mesial temporal lobe including the amygdala following the excision of the left anterior temporal lobe is a parsimonious explanation. Thus, prior to operation the ictal focus in the left anterior temporal lobe has an inhibitory effect on the functioning of right anterior temporal lobe structures, including the amygdala. Following the excision of the noxious inhibitory lesion the components of the right amygdala/anterior temporal lobe can process affective stimuli more efficiently and thus discrimination of emotional expressions of fear improves. As discussed earlier the concept of interhemispheric inhibition from an ictal focus receives support from functional imaging and neurophysiological studies.(Hugg, Kuzniecky et al. 1996; Cendes, Andermann et al. 1997; McIntyre and Poulter 2001; Wilder 2001; Khalilov, Holmes et al. 2003). As mentioned earlier, neuropsychological studies have in addition, demonstrated behavioural effects of such putative metabolic and neurophysiological normalisation following ATL. This is the first demonstration that a similar process can occur in emotional perception.

Some post-operative change on the left may also contribute to improvement in function, such as normalization of left frontal function. However this is not likely to play a major

role as there is little to suggest that the left frontal lobe is vital in the processing of the basic emotions, as lesions of this region are not typically associated with impaired detection of the basic emotions (Hornak, Bramham et al. 2003).

It is also possible that the improved discrimination of fear results from the excision of an amygdala which is 'hyperactive' and thus pre-operatively misinterprets faces as signaling fear (Yamada, Murai et al. 2005). This explanation has several weaknesses. Firstly, it implies that the left amygdala has a vital role in the detection of fear, and our earlier findings (in line with most other stuides) more strongly implicate the right amygdala. Secondly, this reasoning would predict similar effects of a tendency to misinterpret faces as signaling fear for a hyperexcitable right amygdala, and a correction of this bias upon excision of the lesion. This was not found in outstudy and thus the model cannot explain our clear laterality findings.

If, as argued, the improvement in the discrimination of fear after a left ATL is due to a release of right amygdala function, then the effect should only be noted in subjects in whom there was pre-operative inhibition of right amygdala function. Thus the effect should only be found among subjects with left amygdala damage (due to sclerosis or focal damage) and not among subjects with no pre-operative amygdala damage. In our cohort of those undergoing left ATL there was two subjects who had a focal lesions which completely spared the amygdala (one centered on the left inferior temporal cortex, and the other on the parahippocampus). These regions, particularly the inferior portion of the temporal lobe, does not have rich connections to the contralateral amygdala and

anterior temporal lobe, and is thus unlikely to exert any direct inhibitory effects on these structures. Thus when the anterior temporal lobe was excised in this subject, release of function in the right amygdala and surrounding structures would not have occured, and thus no improvement in the discrimination of fear would be predicted. In line with this prediction this subject showed among the least change in the discrimination of fear following left ATL, having the second lowest score for improvement. When change scores were expressed in terms of the standard deviations from the mean change score for healthy controls (Z scores) this subject had a Z score closest to zero of all those within the left ATL group, implying this subject had the least overall change in discrimination within the left ATL group. Clearly, any conclusions based on single cases must be made with caution, but the findings are interesting and support our interpretation.

The limitations associated with using raw change scores in assessing post-operative change have led some authorities to recommend the use of standardized regression based techniques which model the change of the operative groups against a clinical comparison group, as mentioned above(Sawrie, Chelune et al. 1996). While this method is ideal for detecting clinically significant change, the focus of this preliminary study was not clinical change but to confirm an *a priori* hypothesis about the effects of the excision of an ictal focus.

8.6 Conclusion.

This study adds an aspect of emotional perception to the list of specific psychological processes that can demonstrate improvement following excision of a noxious inhibitory

lesion. It demonstrates the potential use of this approach in complementing studies of subjects with chronic focal lesions in efforts to establish the neural correlates of social cognitive processes.

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Chapter 9. Developmental models.

9.1 Key findings

1) Early, but not late, damage to the amygdala impairs theory of mind reasoning and results in a loss of emotional enhancement of memory.
2) Damage to the amygdala at either stage of development is associated with deficits in recognizing facial expressions of basic emotions (specifically fear and disgust) and more complex facial expressions.
3) There was evidence of laterality of amygdala function only in the recognition and evaluation of facial expressions of the basic emotions. Damage to the right, but not left amygdala was associated with impaired recognition and evaluation of facial expressions of fear and sadness. In all other domains damage to either amygdala was associated with a similar profile of deficits.
4) Damage to the amygdala is not associated with a specific decrease in empathic skills as assessed by self-report.
5) Excision of the anterior temporal lobe in adulthood has little impact on theory of mind reasoning or the recognition of complex facial expression. However following a left anterior temporal lobectomy the evaluation of facial expressions of fear improves.

9.2 Neuroplasticity.

The aim of the study was to delineate the effects on social cognitive skills of amygdala damage sustained at different stages of development. As such the findings inform theories of neuroplasticity- that is the adaptive structural and functional

changes that occur in the brain as a result of damage (Buchwald 1990)- and the debate surrounding the effects of lesions acquired at distinct developmental stages.

9.2.1. The Kennard principle.

In her seminal primate work, Margaret Kennard demonstrated that the consequences of motor cortex lesions in infancy were less severe than similar injury in adulthood (Kennard 1942). This suggests that early damage can be compensated for by neural and functional adaptation and reorganization. Thus the 'Kennard principle' would predict compensation for subjects who have early amygdala lesions and a better functional outcome compared to those whose amygdala damage is sustained in adulthood.

We found little evidence to support this principle. Early amygdala damage was associated either with more impairment than late damage (in theory of mind reasoning and emotional enhancement of memory), or with a similar degree of impairment (as in emotion recognition). There were however two findings which are in line with the Kennard principle. Firstly, relative to the healthy controls, subjects with late but not early, amygdala damage were impaired in their evaluation of basic emotional expressions, specifically in the discrimination index for all the emotions combined. However, the impairment in the late amygdala damage group was not significantly greater than the early amygdala damage group. Also, when analyses were conducted at the level of individual emotional categories, impairments in evaluating frightened and sad expressions were evident for both the early and late amygdala group. Finally, as discussed earlier the high proportion of subjects with right sided damage in the late amygdala damage group makes it difficult to draw conclusions about developmental

factors from this experiment, given evidence from other lesion studies for the pivotal role of the right amygdala in emotion recognition.

The second finding in support of the Kennard principle comes from the recognition of complex expressions. The late amygdala damage group was more impaired than the clinical and healthy controls in the recognition of complex facial expressions, whereas the early amygdala damage group was impaired relative to healthy controls only. The preponderance of right sided damage in the late amygdala group is unlikely to explain this finding, as we also found that subjects with focal lesions of either amygdala were impaired in the recognition of complex expressions. An alternative explanation is the uniform loss of anterior and mesial temporal lobe structures in the late amygdala damage group, which may themselves be involved in the recognition of complex expressions.

Thus with some caveats, the results do not support the Kennard principle. Nearly all theories which emphasize the resilience of the young brain have studied the effects of lesions of the cerebral cortex, rather than subcortical structures such as the amygdala (Payne and Lomber 2001). Perhaps phylogenetically ancient structures such as the amygdala, when damaged, are less amenable to compensation through neuroplasticity.

9.2.2 Maturational models.

Our findings can be examined in the light of other models of functional development. Some argue that newly emerging functions are related to the maturation of key brain regions. For example, there are links between the maturation of the hippocampus and development of complex memory systems. Structurally the hippocampus shows

dendritic and synaptic development in childhood and myelination in adolescence in the subicular and presubicular regions, key relay zones between the hippocampus and many cortical areas (Benes, Turtle et al. 1994; Seress 2001). This morphological maturation is held to support the emergence of more complex context-rich, declarative forms of memory which are more critically dependent on the hippocampus (Vargha-Khadem, Salmond et al. 2003). Thus children with very early hypoxic –ischemic damage (arising less than one year) to the hippocampus show some impairment of episodic memory which is not evident at an early age but manifests in the middle childhood years as reliance on such declarative memory increases (Gadian, Porter et al. 2000). This principle is also illustrated by a longitudinal study of recognition abilities in monkeys, which found that neonatal hippocampal lesions had no apparent effect on novelty preference at 1 and 6 months but did emerge at 18 months (Resende, Chain-Fourney et al. 2002). Turning to social cognition, this model would posit that some of the deficits associated with amygdala damage would only manifest later in life, as the amygdala fails to mature both structurally and functionally.

Our current results do not directly address this possibility as we assessed only adults and did not study children with amygdala lesions either longitudinally or at different stages of development. However, there are several possible limitations in the use of a maturational model to interpret our findings. Firstly, although there is some elaboration of connections from the amygdala to cortical regions in childhood and adolescence (Cunningham, Bhattacharyya et al. 2002), there is less intrinsic development within the amygdala than in regions such as the hippocampus,. Secondly, a maturational model cannot account for the deficits in theory of mind reasoning associated with early but not late damage. These deficits cannot be

attributed to damage of a structure which supports theory of mind reasoning in adulthood- there is little evidence that the amygdala is a component of the mature theory of mind network (see chapter 6). Thus the deficits we note are not due to a functionally silent amygdala lesion in early childhood becoming manifest only as more complex theory of mind skills go 'on-line'. Rather, our results are best explained by models which emphasize the role of early interactions between brain regions in sculpting mature neural networks.

9.2.3 Interactive specialization.

Donald Hebb argued that recovery from injury in adulthood is likely to be more complete, partly as the neural substrate required to execute established cognitive functions is less extensive in adulthood and thus more likely to be spared by lesions (Hebb 1949). Thus the network of neural structures recruited for a cognitive function in adulthood may differ from the structures that are required to either perform the same function or its cognitive precursors in childhood. This position is supported by functional imaging studies demonstrating an age related increase of focal activation in fewer brain regions during a range of cognitive tasks, including response inhibition, higher order motor control and face processing (Rubia, Overmeyer et al. 2000; Tamm, Menon et al. 2002; Booth, Burman et al. 2003; de Haan, Johnson et al. 2003; Casey, Galvan et al. 2005). Damage to the amygdala in childhood may disrupt the network which supports the performance of key social cognitive skills (or the developmental precursors of these skills) and thus result in deficits which are carried into adulthood. By contrast, damage to the amygdala in adulthood may have no such deleterious effects as a more focal and perhaps exclusively cortical network now supports the skill. Our findings broadly support this view of functional development as a process

of organizing patterns of interregional interactions, articulated by Johnson and others (Johnson 2000).

This model can explain the counterintuitive finding that a structure which is needed to acquire a skill is not used to execute the skill in adulthood. For example, we argue that the amygdala is needed for precursors of theory of mind reasoning, such as directing social attention, primarily through the use of eye gaze, but not needed for such reasoning per se (Tager-Flusberg, Boshart et al. 1998; Tager-Flusberg and Sullivan 2000; Frith and Frith 2003). A subcortical pathway linking the amygdala, with the pulvinar nuclei and the superior colliculus may be critical in this development (Johnson 2005). This pathway carries low spatial frequency information rapidly, allowing the detection of coarse facial features, and complements the slower carriage of high spatial frequency information from faces carried by cortical routes. Intracranial recordings from the amygdala in humans have shown extremely short latency responses to faces in the amygdala, that become selective to expression of fear after 200ms (Krolak-Salmon, Henaff et al. 2004)- and this fast response is attributed to subcortical processing. After this time sustained amygdala activation spreads to the anterio-temporal, orbitofrontal and occipito-temporal cortex, illustrating the influence of subcortical on cortical processing. The amygdala in adults has been found to be responsive to such low, but not high, spatial frequency information from faces in healthy adults (Vuilleumier, Armony et al. 2003). Low spatial frequency features includes coarse facial detail such as the direction of gaze, and the amount of the 'whites' of the eye that is visible (the sclera). The amygdala has been shown to be exquisitely sensitive to such features (Whalen, Kagan et al. 2004), and the correlation

between the amygdala activation and cortical face processing areas is increased during conditions of direct gaze (George, Driver et al. 2001).

This subcortical processing may be particularly important in infancy as the amygdala-pulvinar-collicular pathway is relatively mature in infancy compared to the cortical visual streams (Born, Miranda et al. 2000). The relative maturity of this pathway may explain face-stimulus preference in early infancy, as newborns show this preference only when faces are presented in the temporal visual field, which feeds to the subcortical pathway, and not the nasal field which feeds to the cortical route (Simion, Valenza et al. 1998). Early amygdala damage will disrupt this subcortical route, perhaps negating early face preference. This is likely to have downstream effects on cortical regions which normally receive input from amygdala efferents in infancy. Such regions would be forced to rely on high spatial frequency face information relayed from the less mature cortical pathways, and may thus develop impoverished, in terms of certain facial features, cortical face processing (Johnson 2005). Thus one of the foundations for the development of more complex social cognitive activities may be missing. It is of note that children with autism show a bias towards the use of high rather than low spatial frequency information in face processing. This processing style could represent the developmental consequences of a dysfunctional subcortical processing route, which in turn could reflect subtle early amygdala damage. Failure to acquire normal face processing abilities in those with autism may contribute to impaired theory of mind reasoning- imputed as a core deficit in the disorder (Deruelle, Rondan et al. 2004).

We thus argue that as skills such as orienting to faces develop into the recognition of the basic and complex emotional expressions, and finally into the more abstract ability to reason about emotional states of others, there is a shift from a reliance on amygdala and its cortical interactions to more refined, specific cortical regions. Through producing delayed or deviant social perceptual skills, early amygdala damage may thus produce later delayed or deviant ToM skills.

Interpretation of the loss of emotional enhancement of memory in early but not late amygdala damage presents several challenges. Unlike theory of mind reasoning, functional imaging studies find that the amygdala is an 'on-line' component of the circuitry underlying the encoding and possibly retrieval of emotionally arousing memories (see chapter 3). So why does adult damage to the amygdala not disrupt emotional enhancement of memory? There are several possible explanations. Firstly, the loss of one amygdala in adult life may be compensated for 'on-line' by other structures such as the contralateral amygdala, during the process of encoding and retrieving emotional memories. The loss of an amygdala early in childhood may prevent the development of such bilateral representation of function. Secondly, cognitive compensation may occur with the use of different strategies to achieve emotional enhancement of memory. For example, the presence of normal amygdalae bilaterally during early development in the late amygdala damage group may have allowed the creation of a store of emotional memories ('housed' in structures such as the hippocampus and prefrontal cortex). When the amygdala is damaged in adulthood it is possible that material may be recognized as emotionally charged, even though it may not produce immediate amygdala based arousal and consolidation. The emotionally charged material might however access other similar emotionally

arousing memories. This in turn may produce central arousal, through mechanisms which do not rely on the amygdala, and allow processes of consolidation to occur. Alternatively, if the left amygdala is damaged, subjects may rely more on the visual apprehension of the emotional aspects of a scene when encoding, and if the right amygdala is damaged more reliance may be placed on the accompanying verbal description. Although we argue it is difficult to separate the modalities in the Heuer and Reisburg illustrated narrative paradigm some have found evidence for just such a lateralization of modality encoding using this paradigm (Frank and Tomaz 2003).

Thirdly, neuroanatomical factors may also partly explain the sparing of emotional enhancement of memory in those with late amygdala damage. Although lesions in the early amygdala damage group were less extensive than the anterior temporal lobe excisions in the late amygdala damage group, the difference in lesion extent may belie the extent of functional damage. Epileptogenic activity from an amygdala may establish the presence of a mirror lesion in the contralateral amygdala (McIntyre and Poulter 2001). This has been demonstrated in vitro for isolated hippocampal preparations and a similar process is thought to happen for the amygdala (Khalilov, Holmes et al. 2003). Thus the presence of an epileptogenic amygdala from early development may lead to damage of the contralateral amygdala, in effect creating partial bilateral amygdala damage. Such damage is subtle: there was no evidence of gross contralateral damage in any of the early amygdala subjects, and few had evidence of bilateral epileptiform foci, which would generally act as a contra-indication to unilateral excision. Functional imaging has however demonstrated that an ictal focus in the mesial temporal lobe is associated with distal hypometabolism of interconnected regions, which is reversed on excision of the ictal focus (see chapter

8). By contrast, in the late amygdala damage group the amygdala was structurally normal throughout development and not epileptogenic, and could not create a 'mirror' lesion in the contralateral amygdala. Thus, the sparing of emotional enhancement of memory in the late amygdala damage group may reflect the less extensive functional damage in this group; the loss of emotional memory with early damage conversely may reflect partial bilateral amygdala damage. A major problem for this explanation is that it implies that subjects with early left amygdala damage would show deficits suggestive of partial right amygdala damage in other domains, and this is not supported by our findings on the recognition of facial expressions of the basic emotions.

The presence of an early amygdala lesion may have other neuroanatomic consequences, altering both the patterns of physical and functional connectivity in the brain. The growth of amygdalo-cortical tracts throughout childhood and adolescence has been demonstrated in the rat and it is argued that there may be similar late tract development in the human (Cunningham, Bhattacharyya et al. 2002). It is possible that the presence of an early amygdala lesion- arising either congenitally or in childhood would disrupt such pathways. Such anomalous structural connectivity between the amygdala would be expected to have functional consequences. Interestingly abnormal functional connectivity between the amygdala and other temporal and frontal regions has been demonstrated in Asperger's syndrome (Welchew, Ashwin et al. 2005). In turn this may reflect the presence from birth of a structurally abnormal amygdala which has been reported in autism (see chapter 8).

As the formation of emotional memories requires the coordinated action of medial

temporal structures, this may be particularly vulnerable to such disruption of projections from the amygdala (Richardson, Strange et al. 2004).

There may be a similar developmental gradient with more severe effects of early damage in other domains of social cognition such as moral reasoning and behaviour. Anderson and colleagues describe two patients who sustained prefrontal cortical damage before 16 months (Anderson, Bechara et al. 1999; Anderson, Bechara et al. 2000). Both were broadly cognitively intact but showed abnormal autonomic responses to punishment contingencies, marked deficits in social and moral reasoning and antisocial behaviour, characterized by a disregard for future consequences of actions. By contrast adults with similar prefrontal damage can be socially insensitive and impulsive, but generally do not commit frank antisocial acts with a disregard for, or inability to understand, the rights of others. The authors suggest that the early damage caused a failure to acquire a store of social knowledge which guides appropriate social behaviour.

The prospective study into effects of unilateral temporal lobectomy, as described in chapter 8 further refines our findings and has implications on how adult lesions may exert differential affects on cognition depending upon the dynamic relationship between functional and dysfunctional structures. Moving from a partial pre-operative to total post-operative damage of the amygdala was not associated with any deterioration in theory of mind reasoning. We argue this reflects the lack of an 'on-line' processing role for the amygdala in theory of mind reasoning in adulthood. By contrast excision of amygdala did impact on the evaluation of facial expressions of the basic emotions, specifically fear. This may reflect the effects of excising a

damaged amygdala allowing other interconnected structures, such as the contralateral amygdala, to function better. Thus the prospective study supports our earlier study suggesting that amygdala is not necessary for theory of mind reasoning in adulthood, but the right amygdala is pivotal in the processing of expressions of the basic emotions, especially fear.

9.3 Final conclusions.

Early amygdala damage may impair emotional memory and theory of mind reasoning through a failure to acquire the requisite precursors for these complex skills. Additionally, the presence of an early amygdala lesion may be particularly disruptive to the development of the structural and functional connectivity needed to support skills which require normal interaction between the amygdala and other structures. Late damage does not affect theory of mind reasoning as the amygdala is not needed in adult life for the performance of such abstract reasoning. Emotional enhancement of memory may be spared by late damage due to the use of alternative cognitive strategies to consolidate emotional memories, or the sufficiency of one intact amygdala to consolidate emotional memories. Our finding of impairment in early and late amygdala damage groups in emotion recognition reflects the necessity of the structure for 'on-line' performance of the task. In the recognition of basic emotional expressions this cannot be compensated for by the presence of an intact contralateral amygdala, possibly as the right amygdala is pivotal in the recognition of certain emotional expressions. The study demonstrates the potential of lesion studies to inform models of the development of social cognitive skills through a comparison of the effects of damage acquired at different stages of development.

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A critical period for the impact of amygdala damage on the emotional enhancement of memory?

Abstract—The amygdala is crucial in modulating enhanced memory for emotionally arousing material. The authors provide evidence that unilateral lesions of the human amygdala arising early in development, but not in adulthood, are associated with a loss of the expected superior retrieval of emotionally arousing over neutral material. This adds to evidence for an early critical period in the development of amygdala function.

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Patients with bilateral lesions of the amygdala generally demonstrate a loss of enhanced memory for emotionally arousing material.[1] This complements functional imaging studies that demonstrate an interdependence of the amygdala and other brain regions at encoding for successfully remembered emotionally arousing, but not affectively neutral, material.[2]

One aspect that has not been considered in lesion studies to date is the impact on emotional memory of the stage of development in which the damage to the amygdala is acquired. This is an important factor determining the degree of deficits in other aspects of social cognition, with early damage associated with greater impairment.[3,4] We hypothesized that a similar effect may hold for emotional enhancement of memory, with amygdala lesions acquired early in development having a more deleterious effect than lesions acquired in adulthood.

Methods. All patients had been originally referred to the Regional Neurosciences Centre for assessment of seizures. Inclusion criteria for the early amygdala damage group were a lesion that had the characteristic neuroradiologic features of a dysembryoplastic neuroepithelial tumor (DNET) and congruent clinical history of seizures with no progressive neurologic deficit[5] (see figure E-1 on the *Neurology* Web site at www.neurology.org for examples of patients in each group). These tumors are highly disruptive of neuronal architecture, and the exact age at which they arise is not clear, but many argue for a dysembryoplastic origin in the case of DNETs.[6] The main differential diagnosis is of low grade gliomas, particularly ganglioglioma (which also often arise in childhood).

Damage in adult life to the amygdala occurs as a result of a temporal lobectomy performed as treatment of medically intractable epilepsy. Usually, the excised amygdala shows pathologic changes but can be histopathologically normal. We included 16 such patients (the late amygdala damage group), most of whom also had evidence of a normal volume of the amygdala on preoperative MRI.

Comparisons were made with 12 patients with similar histories of epilepsy arising from focal lesions that spared the amygdala (the clinical control group). Twenty-seven healthy control subjects with no psychiatric or neurologic history disorders were recruited from the local community. Ethical approval was given by the local research ethics committees and all subjects gave informed consent.

The modified Heuer and Reisburg test was used, which contrasts recognition memory for emotionally arousing and neutral narrative material 1 week after its initial presentation.[1] The primary outcome measure was an emotional enhancement index, calculated as a proportion of correct recognition scores for the emotional passage minus neutral passage over combined neutral and emotional passage recognition [100x (emotional − neutral)/(emotional + neutral)]. An index greater than zero implies that emotionally charged material is better recognized than neutral material.

Results. There were no significant differences between the groups in demographic, neuropsychological, or clinical variables (table) except for a lower verbal IQ in the clinical control group relative to the healthy controls.

In the Heuer and Reisberg task, a repeated measures analysis of variance showed main effects for group ($F[3,65] = 8.3$, $p < 0.001$, with all clinical groups impaired relative to healthy controls, $p < 0.05$) and type of material ($F[1,65] = 9.2$, $p = 0.003$, with emotional material recognized better than neutral). The interaction between group and type of material ($F[3,65] = 8.4$, $p < 0.001$) was explored using the index of emotional enhancement. There was a group difference in this index ($F[3,68] = 9.2$, $p < 0.001$). The early amygdala damage group showed less emotional enhancement of memory than all other groups (all $p < 0.001$, Bonferroni corrected) (figure).

All other pairwise group differences were not significant. The clinical and healthy control groups showed the typical pattern of superior recognition of emotionally arousing over neutral material [for emotional vs neutral material: for healthy controls $t(52) = -2.02$, $p = 0.05$; for clinical controls $t(22) = -1.96$, $p = 0.06$]. The late amygdala group showed similar superior recall of emotionally enhanced material, but this did not reach significance: $t(30) = -1.6$, $p = 0.11$. This pattern was reversed in the early amygdala group who demonstrated poorer recognition of emotionally charged relative to neutral material [$t(26) = 2.57$, $p = 0.02$].

Laterality (left vs right damage) was entered with the stage of amygdala damage (early vs late) as fixed factors in a two-way analysis of variance for the index of emotional

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Table *Demographic and neuropsychological details of participants*

	Early amygdala damage group	Late amygdala damage	Clinical controls	Healthy controls	Tests of significance
Side of damage, right:left	4:10	12:4	4:8	N/A	$\chi^2 = 81.6, p < 0.001$
Male:female	6:8	9:7	5:7	14:13	$\chi^2 = 0.82, p = 0.83$
Age at testing, y, mean (SD)	32 (10)	37 (10)	29 (8)	37 (11)	$F = 2.4, p = 0.91$
Age at seizure onset, y, mean (SD) range	11 (9) 1 to 26	16 (11) 1 to 38	16 (6) 7 to 18	N/A	$F = 0.87, p = 0.43$
Seizure frequency	8.2 (7.8)	4.3 (7.4)	9.8 (8.3)	N/A	$F = 2.1, p = 0.14$
Verbal IQ, mean (SD)	98 (15)	98 (15)	89 (14)	105 (13)	$F = 3.6, p = 0.02$*
Logical memory–	6.1 (2.8)	7.8 (3.2)	8.6 (4.1)	N/A	$F = 1.9, p = 0.16$
Immediate Delayed	6.2 (2.6)	7.8 (3.6)	9.4 (4.0)	N/A	$F = 2.8, p = 0.08$
Heuer and Reisberg task					See text for results
Neutral, mean % (SD)	40.5 (7.2)	37.3 (12.0)	38.5 (8.8)	49.4 (14.1)	
Emotional, mean % (SD)	32.6 (8.7)	45.3 (15.3)	46.7 (11.4)	57.1 (14.0)	

Clinical groups completed the vocabulary, digit span, comprehension, and similarities subscales for verbal IQ, and the block design and object assembly subscales for performance IQ from the Wechsler Adult Intelligence Scale, third revision UK version. An estimate of IQ was obtained from the National Adult Reading test for the neurologically intact control subjects. Memory was assessed with the immediate and delayed logical memory test from the Wechsler Memory Scale, third version (1997), scaled scores are given. Seizure frequency refers to the total number of all types of seizure each month.

* Clinical controls<healthy controls $p = 0.01$.

NA = not applicable.

enhancement. There was no main effect for side of damage [$F(1,26) = 0.33, p = 0.57$] and no interaction between side of and stage of damage [$F(1,26) = 1.9, p = 0.18$], but again a main effect of stage of damage emerged ($F[1,26] = 12.1$, $p = 0.002$).

There was no significant correlation with the age at onset of habitual seizures and index of emotional enhancement for the clinical groups (Pearson's rho = 0.22, $p = 0.16$), suggesting that an early age at onset of seizures per se, regardless of the location of the epileptogenic focus, did not account for the findings. The pattern of results was not accounted for by group differences in age, verbal IQ, standard measures of declarative memory, or seizure frequency, none of which correlated significantly with the index of emotional enhancement.

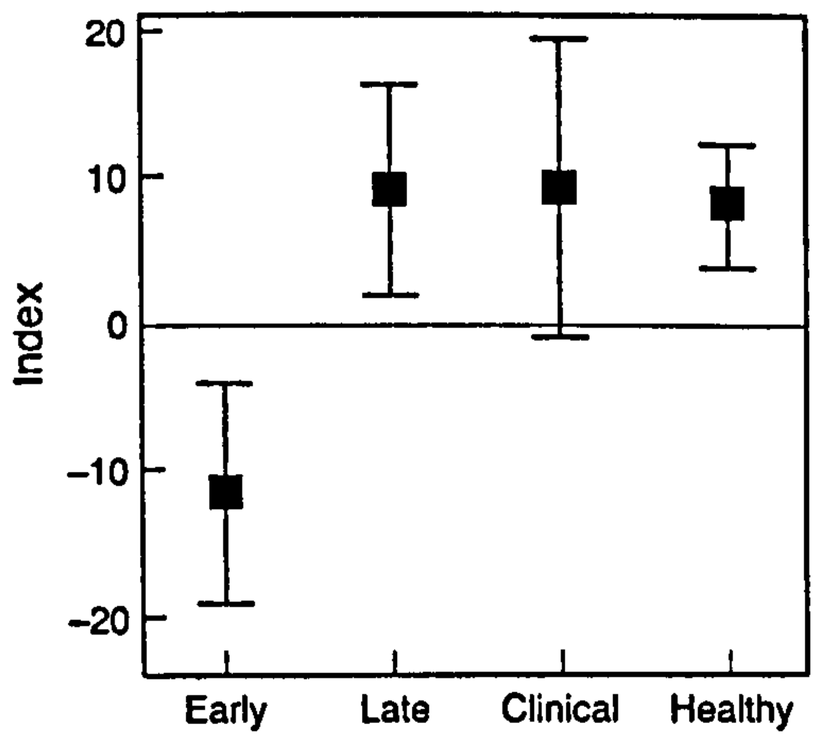

Figure. Showing the mean index of emotional enhancement for each group (with 95% CI). Early = early amygdala damage group; late = late amygdala damage group; clinical = clinical control group; healthy = healthy control group.

Discussion. There was a loss of emotional enhancement of declarative memory in patients with early, but not late acquired, unilateral lesions of the amygdala. As a group, those with early amygdala damage showed better recognition of neutral over emotionally arousing material, a reversal of the usual effects of affective tone on memory.

We can speculate about the mechanisms underlying this phenomenon. The presence of early amygdala damage may disrupt the formation of tracts linking the amygdala to other structures involved in the formation of emotional memories. Indeed the neuroanatomic sequelae of early damage may be more profound than the effects of the circumscribed severing of tracts that occurs following surgery. It may even be the case that early damage allows for emotive material to be suppressed by unopposed frontal systems.[7]

Previous studies of unilateral temporal lobectomy patients have found no clear evidence of laterality effects when using the Heuer and Reisberg stimuli,[8] although particularly detrimental effects of left sided damage have been reported using other emotional memory paradigms.[9] We did not find any laterality effects although there is a risk of a type II error given the small number of subjects. The small sample size also prevented an exploration of higher order interactions of other factors held to be important in

emotional memory such as sex and the type of material to be memorized (whether pertaining to central or peripheral details). Misclassification bias is possible in the early amygdala damage group as most did not have histopathologic confirmation of a DNET. However all had typical clinical histories and while the exact predictive validity of preoperative MR appearances of a presumptive DNET is not established, retrospective studies suggest that several neuroradiologic features (present in our early amygdala subjects) are strongly associated with its presence.[5] Although we did not collect behavioral or neurophysiologic measures of arousal at time of encoding, we propose that the stimuli were not perceived as affectively neutral at time of encoding, as retrieval for the different sections of the narrative was not equal, but showed a significant deficit for the emotionally arousing material. Also, previous studies on patients with bilateral amygdala damage showed normative arousal ratings of the same stimuli.[1,10] Finally, the presence of different types of underlying pathologies and differing extent of lesions also may complicate interpretation.

This study provides further evidence for a sensitive or critical period in the development of cognitive skills that are mediated in part by the amygdala.

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Differential Effects of Lesions of the Amygdala and Prefrontal Cortex on Recognizing Facial Expressions of Complex Emotions

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Abstract

■ Humans can detect facial expressions of both simple, basic emotions and expressions reflecting more complex states of mind. The latter includes emotional expressions that regulate social interactions ("social expressions" such as looking hostile or friendly) and expressions that reflect the inner thought state of others ("cognitive expressions" such as looking pensive). To explore the neural substrate of this skill, we examined performance on a test of detection of such complex expressions in patients with lesions of the temporal lobe (n = 54) or frontal lobe (n = 31). Of the temporal group, 18 had unilateral focal lesions of the amygdala and of the frontal group, 14 patients had unilateral lesions of the ventromedial prefrontal cortex—two regions held to be pivotal in mediating social cognitive skills. Damage to either the left or right amygdala was associated with impairment in the recognition of both social and cognitive expressions, despite an intact ability to extract information relating to invariant physical attributes. Lesions to all of the right prefrontal cortex—not just the ventromedial portions—led to a specific deficit in recognizing complex social expressions with a negative valence. The deficit in the group with right prefrontal cortical damage may contribute to the disturbances in social behavior associated with such lesions. The results also suggest that the amygdala has a role in processing a wide range of emotional expressions. ■

INTRODUCTION

Lesion studies have contributed greatly to the delineation of the neural substrate of components of social cognition, including the ability to recognize what another person might be feeling on the basis of their facial expression. Damage to the amygdala has been consistently linked with deficits in the recognition of emotional expressions (Stone, Baron-Cohen, Calder, Keane, & Young, 2003; Adolphs, Baron-Cohen, & Tranel, 2002; Adolphs, Tranel, Damasio, & Damasio, 1995). This complements amygdala activation observed through neuroimaging studies when healthy subjects are shown faces depicting a range of emotional expressions or social attributes (Zald, 2003; Winston, Strange, O'Doherty, & Dolan, 2002; Baron-Cohen, Ring, et al., 1999). Similarly, both lesion and functional neuroimaging studies implicate the prefrontal cortex (PFC) in the recognition of emotional expressions (Wager, Phan, Liberzon, & Taylor, 2003; Eslinger & Damasio, 1985).

There is no universally accepted typology of emotional expressions, but one widely used division separates the six basic emotions (fear, sadness, disgust, anger, surprise, and happiness) from more complex emotional expressions. The complex emotional expressions can be further divided into "social expressions," which intimately regulate social behaviors, and "cognitive expressions," which reflect the inner thought state of an individual. The social expressions can only be understood in a social context and typically have a clear valence, either positive (e.g., "friendly") or negative (e.g., "hostile" or "contemptuous"). Cognitive expressions, by contrast, provide a display of the inner thought state of an individual, and do not have such a clear valence (examples are looking "pensive," "thoughtful," or "contemplative"). Support for this division comes partly from studies of patients with amygdala lesions, who are impaired in the recognition of social, but not cognitive, expressions (Adolphs, Baron-Cohen, et al., 2002). The further division of the social expressions on the basis of valence receives support from studies suggesting that the right hemisphere processes stimuli with a negative valence which evoke avoidance behaviors, and the left hemisphere processes stimuli with a positive valence which evoke approach behaviors (Mandal et al., 1999; Davidson, 1992a, 1993). The question arises as to whether a similar interaction of valence with laterality may also be found in the detection of more complex social and cognitive expressions.

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Previous lesion studies into the recognition of complex emotional expressions have several limitations. Firstly, many of the patients with amygdala damage that have been reported had extensive damage to surrounding structures, which may themselves play a role in the recognition of facial expressions of emotions. To disentangle the contribution of the amygdala from its adjacent structures, we compare directly the performance of patients with focal lesions of the amygdala with patients with focal lesions that completely spare the amygdala.

Similarly, the relative contribution of different regions of the PFC in the recognition of complex emotional expressions is unclear. Many lesions studies implicate the ventromedial prefrontal cortex (VMPFC) in not only in the recognition of emotions, but also in subjective emotional experience, social behavior, and decision making (Hornak et al., 2003; Tranel, Bechara, & Denburg, 2002) Functional neuroimaging studies have demonstrated activation of regions of the VMPFC, specifically the orbito-frontal cortex (OFC), as healthy subjects make social judgments on the basis of external appearance (O'Doherty et al., 2003; Winston et al., 2002). However, other lesion studies suggest that the dorsolateral prefrontal cortex (DLPFC) may also be involved in recognition of complex social stimuli (Mah, Arnold, & Grafman, 2004; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003). In the present study, we thus aimed to characterize deficits in the recognition of facial expressions associated with unilateral lesions of different regions of the PFC.

The paradigm we used was the revised version of the "Reading the Mind in the Eyes" task (abbreviated to the "Eyes task"). (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997). This requires subjects to detect the mental states of another on the basis of expressions around the eye region. It includes items which depict cognitive and social expressions, both positive and negative in valence. The task benefits from a knowledge of the neural substrate supporting its performance in healthy subjects derived from both functional imaging and ERP studies and is complemented by the "Reading the Mind in the Voice" task (Sabbagh, Moulson, & Harkness, 2004; Rutherford, Baron-Cohen, & Wheelwright, 2002; Baron-Cohen, Wheelwright, Stone, & Rutherford, 1999).

In light of previous studies, we hypothesized that:

1. Patients with focal damage to the amygdala, but not the surrounding structures, would be impaired in the recognition of all complex facial expressions. We predicted a particularly severe deficit in the recognition of social, rather than cognitive expressions.

2. Damage to the PFC would also be associated with specific deficits in the recognition of social rather than cognitive expressions. Within the PFC, it was expected that damage to the VMPFC would be associated with more severe impairments than damage to the DLPFC.

3. Finally, we examined the effect of valence of the stimuli on recognition. We predicted that patients with right-sided damage would show poorer recognition of stimuli with a positive valence, and patients with left-sided damage would show poorer recognition of stimuli with a negative valence.

RESULTS

There were no significant group differences in sex balance ($\chi^2 = 1.6$, $p = .8$), verbal IQ [$F(4,166) = 2.0$, $p = .09$], or age of onset of epilepsy in the patient groups [$F(3,60) = 0.17$, $p = .91$]. There was a significant group difference in age at time of testing [$F(4,171) = 2.5$, $p = .05$], although post hoc analyses with Bonferroni correction did not show any significant pairwise group differences.

There was also no significant difference between groups who completed the control task of gender identification, with all groups performing near ceiling [$F(2,143) = 1.3$, $p = .27$]. For the lesion groups there was no difference between the subgroups and healthy controls in the Benton Facial Recognition test [$F(3,75) = 2.4$, $p = .08$].

Initial analyses examined the performance on the component parts of the "Eyes task" in the right temporal (RT), left temporal (LT), right frontal (RF), left frontal (LF), and healthy control groups. The category of Expression was entered as the within-subjects factor in a repeated-measures ANOVA, using the divisions discussed earlier: cognitive (e.g., contemplative, daydreaming), positive social (e.g., friendly, flirtatious), and negative social (e.g., hostile, accusing) emotional expressions.

There was a main effect of group [$F(4,171) = 10.4$, $p < .001$]. Post hoc comparisons with Bonferroni correction showed that the RT ($p < .001$), LT ($p = .001$), and RF ($p = .03$) groups all scored lower than the healthy controls. In addition, the RT group was impaired overall relative to the LF group ($p = .008$). There was a main effect of category of expression [$F(2,342) = 5.2$, $p = .006$]. Post hoc tests showed better performance for the positive social expressions compared with both the negative social expressions ($p = .03$) and cognitive expressions ($p = .03$). There was a near-significant interaction between expressions category and group [$F(8,342) = 1.85$, $p = .07$], which was further explored with one-way ANOVAs within each category of expressions (results are shown in Table 1).

There were significant group differences in all the component parts of the "Eyes task." In the recognition of cognitive expressions, the RT group was impaired relative to the healthy controls and LF group and the LT group was significantly impaired relative to healthy controls. There was a marked effect of valence in the

Table 1. The Mean Scores (Standard Deviations) for Each Group in the Recognition of Components of the "Eyes Task"

	RT	*LT*	*RF*	*LF*	*HC*	*One-Way ANOVA*	*Post Hoc Comparisons (Bonferroni Correction)*
Cognitive	57 (16)	66 (16)	68 (16)	74 (13)	77 (13)	$F = 12.8, p < .001$	RT, LT < HC ($p < .001$); RT < LF ($p = .002$)
Social—positive	61 (28)	69 (24)	78 (23)	83 (21)	81 (19)	$F = 5.1, p = .001$	RT < HC ($p = .001$); RT < LF ($p = .03$)
Social—negative	67 (28)	69 (26)	56 (25)	73 (20)	76 (19)	$F = 3.7, p = .006$	RF < HC ($p = .01$)

RT = right temporal damage group; LT = left temporal damage group; RF = right frontal damage group; LF = left frontal damage group; HC = healthy control group.

recognition of social expressions. The RT group was impaired in recognizing positive social expressions and the RF group was impaired in negative social expressions.

The Specific Contribution of the Amygdala

To define the specific contribution of the amygdala, patients with focal amygdala lesions ($n = 18$) were compared with patients with focal lesions of the temporal lobe that completely spared the amygdala ($n = 13$) and the healthy controls ($n = 91$). Nonparametric tests were used as the data for each group were not normally distributed and there were unequal group sizes. There were significant group effects in overall performance and in the recognition of cognitive expressions, but no significant group difference in the detection of social expressions—neither negative nor positive (see Table 2).

Pairwise Mann–Whitney *U* tests showed that the right focal amygdala group was significantly impaired relative to healthy controls in overall performance and in the detection of cognitive, but not social, expressions. There was a trend for impairment in the focal left amygdala group relative to the healthy controls in overall performance and a tendency to be poor at identifying cognitive expressions. There were no significant differences between the focal nonamygdala lesion group and healthy controls.

In summary, the deficits were only apparent in patients with focal amygdala damage. Lesions of the temporal lobe, which spared the amygdala, did not produce significant impairments relative to healthy controls. The deficits were present in overall performance, but were more pronounced for the cognitive expressions.

Frontal Lobes: The Specific Contribution of the Dorsolateral and Ventromedial Prefrontal Cortices

To assess the effect of side and exact site of damage patients were initially categorized according to the main site of damage as either right DLPFC ($n = 6$), left DLPFC ($n = 3$), right VMPFC ($n = 8$), left VMPFC ($n = 6$), and healthy controls. Patients with extensive damage to both areas ($n = 8$) were excluded from this analysis. A Kruskal–Wallis test showed an overall significant difference in total scores between groups ($\chi^2 = 11.9, p = .01$). Paired Mann–Whitney *U* tests with Bonferroni correction for multiple comparisons were made and showed a significant impairment in the right DLPFC relative to the healthy controls only ($p = .003$), with no other group differences surviving the adjustment for multiple compar-

Table 2. The Median Scores for Patients with Focal Amygdala Damage and Comparison Groups of Subjects with Focal Lesions which Spared the Amygdala and Healthy Controls

	R Amygdala	*L Amygdala*	*R Focal Lesion (Sparing Amygdala)*	*L Focal Lesion (Sparing Amygdala)*	*Healthy Controls*	*Kruskal Wallis—$\chi(4)^2$ (p value)*	*Pairwise Group Comparisons*
Overall score	69	61	72	71	78	16.4 ($p = .003$)	RA < HC ($Z = -2.8, p = .005$); LA < HC ($Z = -2.5, p = .013$)
Cognitive expressions	47	60	73	67	80	20.5 ($p < .001$)	RA < HC ($Z = -3.6, p < .001$); LA < HC ($Z = -2.4, p = .01$)
Social—positive valence	60	60	80	80	80	7.6 ($p = .11$)	N/A
Social—negative valence	83	67	83	67	83	2.3 ($p = .66$)	N/A

RA = right amygdala damage; LA = left amygdala damage; HC = healthy controls.

isons. There were no group differences in performance of each of the subdivisions (cognitive or social expressions).

To complement this analysis, overlay maps were created of the lesions in patients who were severely impaired on the "Eyes task" (see E-Figure 2 at the Web link www.em-online.org/JOCN). There were six patients with severe impairment (defined as two standard deviations less than the healthy controls): five with right-sided damage and one patient (f24) with left-sided damage. Among the patients with right-sided damage, there were areas of overlap in at least two patients in all of the regions of the PFC. Overlap between three patients occurred on the lateral aspect of the PFC.

A further three patients with right-sided damage (f1, f2, f14) had mild impairment—all with Z scores of −1.38. As can be seen from the reconstructions of the frontal lesions of each patient (see E-Figure 1 at the Web link www.em-online.org/JOCN), these three patients similarly had involvement of all three regions of the PFC.

As there are some similarities between the "Eyes task" and tasks of theory of mind (ToM) reasoning, patients whose lesions overlapped with the peak activations reported in fMRI studies were compared with the patients with damage to other regions of the PFC and healthy controls. Eighteen patients had lesions which involved at least one of the peak activations reported within the medial PFC (f3, f5, f6, f7, f8, f10, f13, f16, f18, f20, f21, f22, f25, f30, f31, f26, f27, f28, f29). The mean total score of those with no "ToM" area lesion was 71 (*SD* 12) and the mean score for the group with no involvement was 67 (*SD* 10). The difference between the groups was not significant [$t(29) = 1.1, p = .28$]. There were no significant differences in the recognition of the cognitive or social expressions (all $p > .1$).

Thus, for the frontal-damage patients, there was a clear effect of side, but not site, of damage. Contrary to predictions, damage to the VMPFC was not specifically associated with impairments in detecting complex cognitive or social expressions. Damage to each of the regions was found among the patients who were most severely impaired. Indeed, when grouped by the main site of damage, involvement of the right DLPFC was associated with an overall impairment in the detection of complex mental states relative to healthy controls.

Table 3. Spearman's Correlations between Overall Performance and Age at Testing, Age of Onset of Epilepsy, and Verbal IQ

	Age	*Age of Onset of Epilepsy*	*IQ*
Temporal lobe damage	−0.2 ($p = .15$)	−0.29 ($p = .03$)	0.37 ($p = .007$)
Frontal lobe damage	0.07 ($p = .71$)	0.007 ($p = .99$)	0.45 ($p = .01$)
Healthy controls	−0.22 ($p = .08$)	–	0.12 ($p = .35$)

change in the overall pattern of results. For overall scores, the main effect of group remained [$F(4,161) = 9.1$, $p < .001$] with post hoc Bonferroni comparisons showing deficits relative to healthy controls in the RT ($p < .001$) and LT groups($p = .034$). The RF group remained impaired in the detection of negative valence stimuli relative to healthy controls [$F(4,161) = 2.6$, $p = .04$; RF < HC $p = .03$].

The age of onset of habitual epilepsy was also considered, and there was no overall correlation across all groups with performance (Pearson's rho = −.19, $p = .12$) or within each subgroup. To assess the possible impact of diverse etiology on performance, the frontal lesion patients were divided on the basis of the clinical indication for the frontal resection (intractable epilepsy, focal tumor, or arteriovenous malformation) as noted above. There was no significant difference between these groups in overall performance (Kruskal–Wallis $\chi^2 = 3.39$, $p = .18$). For the temporal lesion patients, the underlying cause of medically intractable epilepsy present in all cases was also considered comparing patients with underlying mesial temporal sclerosis with all other pathologies. Again, there was no significant effect on performance of underlying etiology (Mann-Whitney u; z = −1.0, $p = .30$).

Effects of Possible Moderating Variables

Correlations between the overall performance in the detection of complex cognitive and social expressions and age, estimated IQ, and age of onset of epilepsy where applicable are shown in Table 3.

The main analyses were conducted with estimated IQ entered as a covariate as it was significantly associated with performance in the temporal lobe group and other studies have reported a modest association between verbal IQ and performance in the task among healthy controls (not found in this study). There was little

DISCUSSION

We tested patients with either prefrontal cortical or temporal lobe damage on the ability to recognize social and cognitive expressions, using the "Reading the Mind in the Eyes" task (Baron-Cohen, Wheelwright, Hill, et al., 2001). The primary findings indicate that anterior temporal lobe damage is associated with impairments in the recognition of expressions of cognitive and social expressions. This occurs despite an intact ability to extract other forms of information relating to nonemotional attributes such as gender from the same stimuli. Within the anterior temporal lobe, the amygdala appears

to mediate this affective processing. Focal damage to structures which spare the amygdala led to performance that did not differ significantly from healthy controls. Although there was a suggestion that focal right amygdala damage was associated with more profound impairments than focal left amygdala damage, the results did not support a clear lateralization of function at this subcortical level. Contrary to expectations, damage to the amygdala and anterior temporal lobe was more strongly associated with impaired recognition of cognitive, rather than social, expressions.

This is in marked contrast to effects of lesions of the PFC. Deficits were only present among those with right prefrontal cortical damage, and contrary to our expectations, were as marked in those with dorsolateral as orbito-frontal or medial damage. The deficits among the right prefrontal damage patients were confined to the recognition of negative social expressions.

The Effects of Damage to the Amygdala

This study provides evidence of a specific contribution of the amygdala, as opposed to closely associated structures, in the recognition of facial expressions of states other than the basic emotions. This is a significant finding as previous studies into the effects of unilateral amygdala damage have typically used patients with extensive surgical damage to the anterior and medial-temporal lobe and had varying degrees of damage to the amygdala itself (Brierley, Medford, Shaw, & David, 2004; Adolphs, Tranel, et al., 2001; Boucsein, Weniger, Mursch, Steinhoff, & Irle, 2001; Anderson, Spencer, Fulbright, & Phelps, 2000). Indeed, Adolphs, Tranel, et al. (2001) reported only a weak correlation between the extent of amygdala damage and the deficits in emotion perception. Another study of a small number of patients with focal lesions incorporating the amygdala did not find the patients to be severely impaired in the recognition of emotions, unlike patients who had more diffuse mesial temporal lobe sclerosis (Meletti et al., 2003). Our demonstration of clear impairments in the recognition of complex social and cognitive expressions benefits from the relatively large number of patients included and the relative uniformity of the underlying pathology of the amygdala lesion.

The current study replicates a previous report of deficits in the decoding of cognitive and social expressions among patients with damage to either amygdala (Adolphs, Baron-Cohen, et al., 2002), This study further found evidence of a selective deficit among patients with amygdala damage in the recognition of social, but not cognitive, expressions. Our results show the opposite pattern, with more severe impairment in the recognition of cognitive expressions. It is unlikely that the differences are due to factors in the design, as both studies used the same stimuli. Factors relating to the participants are more likely to account for the differences. For example, in the Adolphs et al. study, the patients had variable amounts of amygdala damage, unlike the uniform total excision in the anterior temporal lobectomy patients we studied.

The amygdala plays an important role in interpreting eye gaze, and deficits in recognition of facial expressions of basic emotions such as fear can be ameliorated when patients are guided in making eye contact within the face (Adolphs & Tranel, 2003). Thus, the patients with amygdala lesions in this study may simply not have been performing the task normally, perhaps scanning the stimuli in a highly aberrant manner. As we did not track the eye movements of patients during the task, we cannot exclude this possibility. However, two findings suggest that the patients were processing the stimuli to some degree. Firstly, the patients with amygdala damage were intact in the control condition and were thus able to extract information relating to a nonemotional, physical property. Secondly, the patients were not significantly impaired in the recognition of social expressions, relative to those with focal nonamygdala damage. However, future studies with patients who have lesions of the amygdala would benefit from detailed examination of how patients scan the stimuli.

The Effects of Prefrontal Damage

The results in patients with prefrontal damage have several notable features. Deficits were found almost exclusively in patients with right prefrontal cortical damage. There was a marked effect of valence with the impairment in the right frontal groups confined to social expressions with a negative valence. This loss of sensitivity to negative valence social signals can be placed in the context of other social cognitive sequelae of damage to the right PFC. Marked behavioral disinhibition and social insensitivity has been reported with right, but not left, PFC damage (Gomez-Beldarrain, Harries, Garcia-Monco, Ballus, & Grafman, 2004; Tranel et al., 2002; Kolb & Taylor, 1981). Our finding of a failure to recognize negative social expressions might partly explain the social insensitivity and behavioral disinhibition found after right prefrontal cortical damage.

It has been argued that the right hemisphere is dominant for positive emotions and the left hemisphere is dominant for negative emotion (Davidson, Jackson, & Kalin, 2000; Davidson, 1992b). We report that damage to the right PFC is associated with poorer recognition of negative social expressions, which might prompt withdrawal behavior. However, we did not find impairments in the recognition of positive social expressions (which might motivate approach behavior) in the patients with left prefrontal cortical damage. In part this may reflect the psychometric properties of the test as the positive emotional expressions were significantly easier to identify and a ceiling effect may have thus masked subtle deficits among the left prefrontal cortical damage group.

Table 4. Basic Demographic and Neuropsychological Details for Each Group

	Sex (M:F)	*Age, yrs*	*Onset of Epilepsy, age*	*IQ*	*Benton Facial Recognition Task*
Right temporal	11:16	37 (11)	16 (11)	102 (14)	43.2 (3.0)
Left temporal	10:17	32 (10)	14 (13)	103 (14)	43.3 (4.7)
Right frontal	8:8	41 (15)	16 (22)	105 (13)	45.9 (4.6)
Left frontal	8:7	39 (14)	15 (10)	112 (8)	46.0 (3.8)
Healthy controls	43:48	34 (12)	–	107 (10)	–

Mean and standard deviation are given for each continuous variable.

In its present format the valence of the distracter items in the "Eyes task" is not systematically manipulated (thus, some items had purely positively or negatively valenced distracters and some had a valence mix). Future versions might manipulate the valence of the distracters to test for the possibility of a general bias in choosing positively valenced descriptors in right and negatively valenced descriptors among left prefrontal cortical damage patients.

There are other possible interpretations of the finding of right-sided processing of complex social expressions that may relate to the nature of the stimuli. Facial expressions of the basic emotions, such as fear, disgust, and anger, are held to be cross-cultural signals, which do not depend upon social knowledge for their interpretation and which may be detected by dedicated innate neural circuits (Ekman, 1992; Ekman, Sorenson, & Friesen, 1969). By contrast, social expressions are defined with reference to social situations and understanding, and their detection will rely in part on social knowledge and prior experience (Baron-Cohen, Wheelwright, Hill, et al., 2001). The right PFC has been associated with both episodic and autobiographical memory processes, which may be recruited when retrieving social and personal knowledge necessary for decoding social expressions (Fink et al., 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). There is also some evidence of more extensive activation of the right PFC when scenes are viewed which evoke moral emotions such as outrage (Moll et al., 2002). Although the stimuli used to evoke moral emotions were of complex interpersonal scenes, they share with the stimuli we

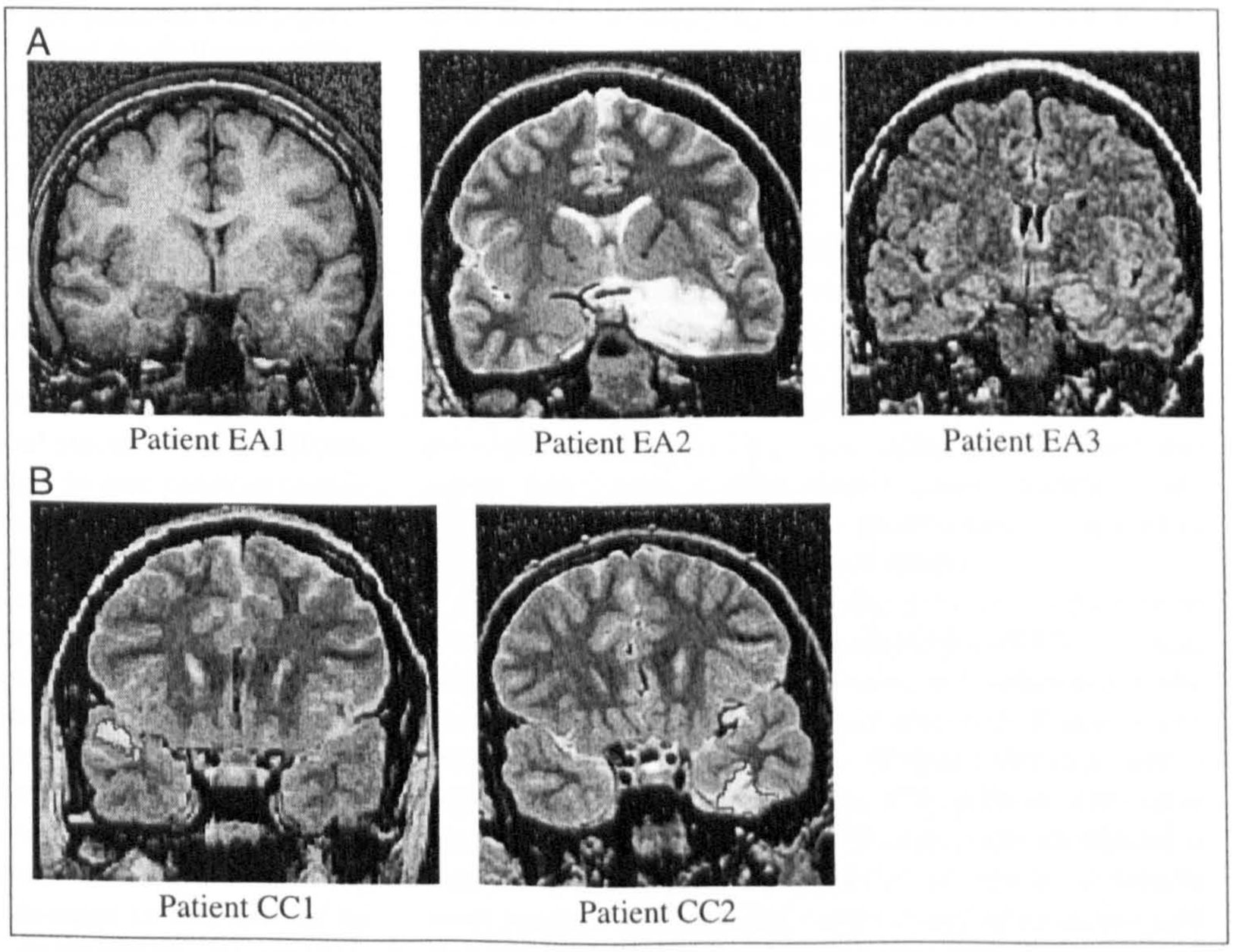

Figure 1. Selected MR images of patients in the early amygdala damage and clinical control groups. (A) Three patients in the early amygdala damage group are shown. Patient EA1 had the smallest lesion of this group seen as a hyperdense lesion on T1 sequence in the superolateral portion of the left amygdala (indicated by the red line). Patient EA2 had a large lesion centered on the amygdala extending toward the temporal pole and incorporating the anterior hippocampus. The presence of a DNET was confirmed when the patient proceeded with the operation. Patient EA3 has gross enlargement of the left amygdala, seen best on the FLAIR sequence. (B) Two patients in the clinical control group. Patient CC1 had a lesion in the right temporal operculum. Patient CC2 had a lesion lying in the antero-inferior aspect of the right anterior temporal lobe.

used the property of a reliance on social knowledge and experience for interpretation. This account has the advantage of placing the social perceptual deficits in the context of broader problems with social cognition. However, it does not account for the sensitivity to valence of the complex mental state we report.

Contrary to our prediction, we did not find more severe impairments on the "Eyes task" among patients with orbito-frontal or medial damage, relative to those with dorsolateral prefrontal cortical damage. Indeed, the group with most severe deficits had predominant damage to the right DLPFC, although the small number of patients in this group means this finding needs to be interpreted with caution. The findings are perhaps surprising given the wealth of lesion and neuroimaging evidence mentioned earlier, which implicates the VMPFC in the recognition of emotional expressions and other social cognitive processes. However, there have been other findings of a lack of correlation with selective damage to the VMPFC and deficits in tasks held to be mediated by this region—such as affective decision making as indexed by the Iowa gambling task. Indeed, one large study found that damage to the right DLPFC correlated more strongly with deficits on the task than damage to the VMPFC (Clark, Manes, Antoun, Sahakian, & Robbins, 2003), with the best overall predictor of faulty emotional decision making being the total amount of damage to the entire PFC. In a recent large lesion study, Mah et al. (2004) have reported that lesions of either the DLPFC or OFC were associated with impairments in social perception (Mah et al., 2004). A previous study which included nearly all the patients who participated in the "Eyes task" also failed to find any differential effects of lesion location on ToM reasoning (Rowe, Bullock, Polkey, & Morris, 2001).

The findings from our study may also seem to be at odds with functional neuroimaging in healthy subjects. Firstly, peak activations during performance of the "Eyes task" in healthy subjects have been reported as greater in the left rather than the right PFC (Baron-Cohen, Ring, et al., 1999). Secondly, there is substantial evidence suggesting that the medial PFC is activated when healthy subjects attribute mental states to others (Frith & Frith, 2003). However, damage in our patients to the medial PFC was not specifically associated with impaired performance on the "Eyes task." This was true even when the lesion incorporated regions which are maximally activated in healthy subjects during ToM reasoning. Interestingly, others have reported intact ToM reasoning despite complete loss of regions of the medial PFC held to support such reasoning (Bird, Castelli, Malik, Frith, & Husain, 2004). Overall, the findings suggest that the right PFC acts as an integrated functional system in the detection of complex cognitive and social expressions. Thus, damage to any one of its components (orbito-frontal, dorsolateral, or medial) can lead to impairments.

Limitations of the Study

The "Eyes task" was originally described as an advanced test of ToM on the grounds that it involves the attribution of a relevant mental state (e.g., daydreaming). Clearly, it does not include the second stage of inferring the content of that mental state (e.g., daydreaming *about* an impending holiday) (Baron-Cohen, Wheelwright, Hill, et al., 2001). However, some reserve the term "ToM" for tasks which incorporate both stages. In this article, we therefore use different terminology, dividing the stimuli into cognitive and social expressions. The distinction we employ has proved useful in other neuropsychological studies, although we acknowledge that there are many other ways of classifying the stimuli (Adolphs, Baron-Cohen, et al., 2002).

The "Eyes task" has been analyzed as requiring subjects to have a lexicon which includes cognitive (thought-state), social, emotional, or mental state terms and to know the semantics of these terms. The task involves mapping these terms to the stimuli presented (the eye region of the human face) (Baron-Cohen, Wheelwright, Hill, et al., 2001). The mean score on the "Eyes task" for healthy controls in our study was similar to the normative scores given in the original report of the task (Baron-Cohen, Wheelwright, Hill, et al., 2001). The test has proved to have concurrent validity in that it correlates well with measures of personality traits of empathic understanding (Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004). It is also sensitive to deficits among subjects with Asperger's syndrome who have core deficits in aspects of social cognition such as the accurate detection of mental states (Baron-Cohen, Ring, et al., 1999). However, the control condition used in the task of gender assignment differs in its level of difficulty as there are only two choices, and these choices are fixed throughout (male vs. female). This may have resulted in a partial ceiling effect obscuring group differences. The stimuli were of the human eye region only and static in nature, features which might be criticized for lacking ecological validity. However, previous studies have shown that the detection of complex mental states from the eye region does not differ greatly when the entire face region is used (Baron-Cohen, Jolliffe, et al., 1997) and the eye region is the natural focus of attention when decoding mental states of others.

Although this is one of the largest studies with unilateral focal lesions of the amygdala and PFC in social perception, there is still a risk of type 1 errors when the performance of subgroups are considered. There is also some variability in the extent of exact damage within each group, particularly among the patients with focal lesions of the temporal lobe. This possible confound is less marked in the frontal group, in which all lesions were surgical and defined on the basis of neurosurgical reconstructions of the excised areas, allowing precision in defining the boundaries of the lesion.

Conclusion

This study delineates the involvement of the amygdalae and the right PFC in the recognition of cognitive and social expressions. The amygdala appears to process facial expressions extending beyond the basic emotions into displays of more complex cognitive and social expressions. The study also demonstrates the effects of damage to the right PFC on the detection of negative social expressions. This provides a plausible neurocognitive substrate for the clinical presentation associated with damage to the region.

METHODS

Participants

All patients were recruited from the Department of Neurosurgery at the Regional Neurosciences Centre at King's College London. Demographic and clinical details are given in Tables 1 and 4. Ethical approval was given by the local ethics committees. All participants gave informed consent.

Ninety-one healthy control subjects, with no psychiatric or neurological disorders, were recruited in part from a database of healthy volunteers held at the Institute of Psychiatry.

Patient Groups

Fifty-four patients with temporal lobe damage were tested: 27 had RT damage and 27 had LT damage. Thirty-one patients with frontal lobe damage were included, 16 with RF and 15 with LF damage. The temporal lobe damage group was composed of the following patients (see Figure 1 for images of patients from each group).

The 54 temporal lobe-damaged patients were further divided as follows:

1. 23 anterior temporal lobectomy patients. All patients in this group had en bloc surgical resection of the anterior temporal lobe to treat medically intractable epilepsy. All operations were en bloc resections (8 left-sided and 15 right-sided) with complete excision of the amygdala in all cases.

2. 18 patients with focal amygdala lesions (7 right and 11 left). All patients in this group had focal amygdala lesions, 8 with extension beyond this structure. On the basis of neuroradiological features and clinical histories, these lesions were thought to be indolent nonprogressive tumors such as dysembryoblastic neuroepithelial tumors (DNETs) or gangliogliomas (16 patients) or arteriovenous malformations (2 patients).

3. 13 patients with focal nonamygdala lesions (5 right- and 8 left-sided). All patients in this group had focal lesions of the temporal lobes that completely spared the amygdala. The lesions were made up of indolent nonprogressive tumors (10 patients), and one subject each with an arteriovenous malformation, developmental anomaly, and epidermoid cyst.

Frontal Lobe Patients

The 31 frontal lobe patients all had surgical resections as treatment of medically intractable epilepsy ($n = 11$), vascular malformations ($n = 3$), or tumor excisions ($n = 17$). The groups were further classified according to side and the prefrontal sectors of functional significance into which the lesions predominately encroached. The areas were defined anatomically as DLPFC (Brodmann's areas 9 and 46, including medial portions) or VMPFC (which was taken as including either the orbital or medial PFC, correspomding to, Brodmann's areas 10, 11, 12, and 25). The characterization of this group has been described elsewhere (Hornak et al., 2003; Rowe et al., 2001). These four groups (R VMPFC, L VMPFC, R DLPFC, and L DLPFC) did not differ significantly in terms of estimated IQ ($\chi^2 = 3.3$, $p = .35$) or sex ($\chi^2 = 1.2$, $p = .87$). The extent of the lesions is illustrated in E-Figure 1 at the Web link www.em-online.org/JOCN. In 19 cases, the lesions were reconstructed on the basis of postoperative MR images. In three cases, postoperative MR imaging was not possible due to the presence of intracranial metal clips, and in nine cases, MR images from different neuroimaging centers could not be obtained. In these cases, the neurosurgeon's reconstructions of the resected areas were used.

In addition, overlay maps were created by superimposing the individual lesions of patients who showed impairment on the "Eyes task." Each patient's score was expressed as the number of standard deviations from the mean of the healthy controls (i.e., Z scores). Severe impairment was defined as a Z score < -2. The lesions of these impaired patients were superimposed manually onto a standard brain template. Given the relatively small number of patients who were impaired ($n = 6$) and the unavailability of some postoperative scans on these patients, a voxel-based method of defining lesion overlap was not used (these images of E-Figure 2 can be viewed at www.em-online.org/JOCN).

The "Eyes task" involves the attribution of an emotional or mental state to others. This is arguably a preliminary step to inferring and reasoning about the content of the mental states of others—an ability often referred to as "ToM reasoning." The peak activations reported during the performance in healthy participants of ToM tasks have fallen mainly with the medial PFC (Frith & Frith, 2003). We divided our frontal damage patients on the basis of involvement or sparing of the reported peak areas of activation. The performance of these groups was compared to determine whether lesions of the regions found to support on-line ToM reasoning in fMRI studies were associated with particularly severe impairment in the "Eyes task."

Tasks

All subjects completed the National Adult Reading Test to estimate intelligence (Nelson, 1982). All patients in the temporal lobe damage group and 25 in the frontal damage group also completed the Benton Facial Recognition test as damage to the anterior brain can be associated with facial processing deficits (Benton, Sivan, Hamsher, Varney, & Spreen, 1983).

Experimental Tasks

In the "Reading the Mind in the Eyes" task (revised version)—or "Eyes task"—subjects were presented with pictures of the eye region of actors. The pictures are flanked by four terms (the correct term and three foils) and the subjects were asked to choose which term best describes what the actor is thinking or feeling (Baron-Cohen, Wheelwright, Hill, et al., 2001). The terms do not include any basic emotional descriptors (happy, sad, angry, frightened, disgusted, or surprised). To ensure subjects understood the terms, a glossary of definitions was provided and subjects were encouraged to ask about the meaning of any unfamiliar words. As an additional non-emotional control task, the temporal lobe damage and healthy control groups were asked to judge the gender of the actor, as amygdala damage has been associated with specific impairments in decoding the eye region.

In this study, four independent assessors divided the stimuli into those which depicted cognitive expressions (e.g., "pensive," "daydreaming," "contemplative") or social expressions. The social expressions were then further divided into those with a positive valence (e.g., flirtatious, playful, friendly) and those with a negative valence (e.g., hostile, suspicious, defiant, accusing). Only items on which there was complete agreement on the categorization were included in further analyses. Examples of each of the type of stimuli can be seen on the Web link: www.em-online.org/JOCN, E-Figure 3.

A score of 1 point was given for a correct answer, and 0 for an incorrect answer. Scores were converted to percentages to allow comparisons in the performance across the cognitive and social expressions.

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The impact of early and late damage to the human amygdala on 'theory of mind' reasoning

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Summary

There is a burgeoning interest in the neural basis of the ability to attribute mental states to others; a capacity referred to as 'theory of mind' (ToM). We examined the effects of lesions of the amygdala which arise at different stages of development on this key aspect of social cognition. Tests of ToM, executive and general neuropsychological function were given to subjects with lesions of the amygdala arising congenitally or in early childhood ('early damage', *n* = 15), subjects who acquired damage to the amygdala in adulthood ('late damage' *n* = 11) and matched clinical (*n* = 14) and healthy comparison groups (*n* = 38). Subjects with early damage to the amygdala, particularly if the lesion was associated with childhood onset of seizures, were impaired relative to all other groups on more advanced tests of ToM reasoning, such as detecting tactless or ironic comments or interpreting non-literal utterances. These deficits held for subjects with either left or right early amygdala damage and encompassed the understanding of both the beliefs and emotional states of others. In contrast, subjects who acquired damage to the amygdala in adulthood (usually as part of an anterior temporal lobectomy) were not impaired in ToM reasoning relative to both clinical and healthy controls, supporting the position that the amygdala is not part of the neural circuitry mediating the 'on-line' performance of ToM reasoning. In line with theories which claim that ToM is an independent faculty of cognition, we found that the pattern of results held after co-varying for measures of executive function, memory and general intellectual functioning. We discuss the results in the light of recent theories which link early developmental insults to the amygdala with the ToM impairments which are thought to be a core neurocognitive deficit found in disorders such as autism. We conclude that the amygdala may play an important role in the neural systems supporting the normal development of ToM reasoning.

Keywords: amygdala; theory of mind; autism; executive function

Abbreviations: DNET = dysembryoblastic neuroepithelial tumour; fMRI = functional MRI; IQ = intelligence quotient; ToM = theory of mind

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Introduction

The term 'theory of mind' (ToM) has been applied to the capacity to attribute mental states to others in order to understand and predict their behaviour (Premack and Woodruff, 1978). Several models of the neural circuitry mediating this key aspect of social cognition have already been developed on the basis of functional neuroimaging, human lesions and primate studies. The amygdala has been included in most models of ToM reasoning as part of a distributed network which includes other regions of the temporal lobe (particularly the polar cortex and superior temporal gyrus) and frontal lobes (the orbitofrontal cortex and anterior cingulate cortex) (Brothers, 1989; Stone *et al.*, 1998; Tager-Flusberg *et al.*, 1998; Abu-Akel and Bailey, 2000; Baron-Cohen *et al.*, 2000; Tager-Flusberg and Sullivan, 2000; Adolphs 2003; Frith and Frith, 2003).

Several positions have emerged concerning the exact role of the amygdala in the mediation of reasoning about the mental states of others. First, some theorists place the amygdala at the very core of the neural circuitry which supports ToM reasoning and argue that it is both necessary for the development of the ability to reason about others and a component of the 'on-line' circuitry recruited during per-

formance of ToM tasks (Brothers, 1989; Abu-Akel and Bailey, 2000; Baron-Cohen *et al.*, 2000; Stone *et al.*, 2003). In support of the necessity of the amygdala in the development of ToM abilities, there are case reports of subjects with lesions of either one or both amygdalae which arise early in development who show impairments on a range of tasks requiring ToM reasoning (Adolphs *et al.*, 1998; Heberlein, 1998; Fine *et al.*, 2001). People who have autism consistently have been found to exhibit deficits in ToM reasoning, which are thought to underpin many of the anomalies in social behaviour typical of autism (Baron-Cohen *et al.*, 1985). This has been linked explicitly to structural and, by implication, functional developmental abnormalities of the amygdala, with reports of both macroscopic and microscopic abnormalities (Bailey *et al.*, 1998; Aylward *et al.*, 1999; Baron-Cohen *et al.*, 1999*b*; Howard *et al.*, 2000; Salmond *et al.*, 2003). Similarly, cortical tubers which develop within the temporal lobes during fetal life have been associated with autistic comorbidity among people who have tuberose sclerosis (Bolton and Griffiths, 1997).

Evidence for the necessity of the amygdala in the adult 'on-line' performance of ToM tasks comes from human lesion and functional neuroimaging studies. Stone *et al.* (2003) describe two such subjects who acquired damage to the amygdalae in adult life who are impaired in the attribution of mental states to others on the basis of the appearance of the eye region and also in the ability to detect when a character in a story had unintentionally hurt the feelings of another. Larger group studies have demonstrated acquired deficits in ToM tasks among adult subjects with both left and right hemisphere cerebrovascular insults, which may have compromised the blood supply to the amygdala from the deep perforating branches of the middle cerebral artery (Happe *et al.*, 1999; Channon and Crawford, 2000). The findings of the lesion studies are corroborated to some extent by findings from functional MRI (fMRI). In healthy subjects, the amygdala is activated when judgements are made about the mental states of others on the basis of their appearance (Baron-Cohen *et al.*, 1999*b*; Winston *et al.*, 2002) and when mental states are attributed to the movements of abstract shapes, as in the Heider and Simmel paradigm (Castelli *et al.*, 2002; Schultz *et al.*, 2003).

A second position holds that while the amygdala may support the development of ToM skills, it is not a critical component of the circuitry which supports the 'on-line' performance of ToM reasoning in adulthood. In this vein, Frith and Frith (2003) have highlighted in their synthesis of fMRI studies that although some studies have demonstrated amygdala activation during the performance of ToM reasoning tasks, such studies are the exception rather than the rule. They and other authorities (Tager-Flusberg *et al.*, 1998; Tager-Flusberg and Sullivan, 2000) have argued that the amygdala is more likely to support the development (and on-line performance) of basic social perceptual abilities which are taken to be the precursors or 'protoforms' of ToM knowledge. There is consistent evidence for the activation of the amygdala during the 'on-line' adult perception of basic and complex emotional states and for the deleterious effects of early amygdala lesions on emotional perception (for a review of fMRI studies see Zald, 2003; and for a review of lesion studies see Adolphs, 2002). As skills such as the perception of the emotional states of others develop into the ability to reason about these mental states, there is a concomitant shift from a reliance on phylogenetically ancient structures such as the amygdala to frontal cortical regions. It is argued that without these social perceptual skills, the attainment of ToM skills is at the very least delayed and rendered error prone in contrast to the qualitatively effortless and accurate ToM attributions found in healthy subjects. Thus, in these models, the amygdala is not thought to be necessary for the on-line execution of ToM reasoning; however, its role in supporting the precursors of ToM reasoning may make its integrity a necessary but not sufficient condition for the development of normal ToM abilities.

One way of comparing these two positions is to examine ToM reasoning among subjects who acquire lesions to the amygdala early in development (either congenitally or in early childhood) with those who acquire damage to a normally developed amygdala in adulthood. Both positions would predict that subjects with early damage would be impaired in ToM reasoning. If the amygdala additionally supports adult 'on-line' ToM reasoning, then we would predict similar ToM impairments in subjects with damage acquired in adult life. If, however the amygdala has a purely developmental role and is not involved in the adult 'on-line' execution of ToM reasoning, then we would expect relatively intact ToM performance among those with amygdala damage acquired in adulthood.

A third position argues that the amygdala is only part of the substrate of reasoning about the mental states of others in so far as it supports domain-general cognitive functions (Frye, 1999, 2000). Some have argued that there is no need to invoke a domain-specific ToM module and instead emphasized the frequent presence of executive dysfunction among many subjects with ToM impairments (Channon and Crawford, 2000). However, there are already several case reports, including a subject with an amygdala lesion, suggesting that ToM impairment can occur even in the presence of intact executive function—a dissociation in favour of a modular ToM mechanism (Bach, 2000; Fine *et al.*, 2001; Rowe *et al.*, 2001). Further detailed examination of subjects with focal lesions of the amygdala may shed light on the issue: prominent executive dysfunction, general intellectual and language impairment would not be expected in this group, and thus any deficits in 'ToM' reasoning would not be readily reduced to impairments in other cognitive systems.

Other emergent themes in research on the amygdala include the possible impact of gender and laterality on amygdala function, in domains such as the perception of, and memory for, emotionally salient stimuli (Buchanan *et al.*, 2001; Zald, 2003). For example, two fMRI studies have

reported that enhanced recognition memory for emotionally arousing material correlates with left amygdala activation at encoding in women and right amygdala activation in men (Cahill *et al.*, 2001; Canli *et al.*, 2002). Turning to ToM, there are gender differences, most evident in the acquisition of ToM milestones which are generally attained earlier by girls (Baron-Cohen *et al.*, 1999*a*). In addition, several groups have reported laterality differences in ToM reasoning with prominent deficits among subjects with right, but not left, hemisphere damage (Happe *et al.*, 1999). Other human lesion studies and one functional imaging study report exactly the opposite pattern (Channon and Crawford, 2000). Stone *et al.* (2003) have speculated that there is an effect of the content of the mental state inference on laterality of function. In their *faux pas* task, subject D.R. who had predominantly right-sided amygdala damage was most impaired in affective state attributions, i.e. realizing that a person would feel hurt or insulted when confronted with a tactless comment. In contrast, subject S.E. who had more prominent left-sided amygdala damage made more errors in appreciating that the tactless comment was made unintentionally, thus showing impairment in epistemic or belief attribution. This is similar to the subject described by Fine *et al.* (2001) who had more selective left-sided amygdala damage and was impaired on a range of ToM tasks which assessed mainly epistemic (belief) mental state attributions. We aimed to explore further this possible dissociation of the ability to reason about the epistemic and affective mental states of others.

Previous research into the neural basis of the development of ToM skills is limited by its reliance on case studies, in which damage to the amygdala arises from a range of aetiologies and typically is accompanied by extensive extra-amygdala damage. We attempted to overcome such limitations by studying a large group of subjects with relatively focal pathology of the amygdala. The lesions were thought, on clinical and neuroradiological grounds, to be compatible with the presence of a dysembryoblastic neuroepithelial tumour (DNET) (Raymond *et al.*, 1994, 1995; Honavar *et al.*, 1999). DNETs are composed of bundles of axons lined by small oligodendrocyte-like cells and astrocytes (Daumas-Duport *et al.*, 1988; Honavar *et al.*, 1999). Neurons are relatively sparse and appear to float with random orientation within a mucoid matrix, and have a morphology that occasionally differs from that of normal cortical neurons (Raymond *et al.*, 1994; Honavar *et al.*, 1999). The tumour thus constitutes a major disruption of normal neuronal architecture and function which is reflected in its association with a childhood onset of focal seizures. The neurophysiological abnormalities are often accompanied by metabolic anomalies with the finding of resting hypometabolism in the region of the DNET on fluordeoxyglucose PET. The tumour is also well characterized in terms of its clinical course and preoperative MRI appearances, which allows for a reliable presumptive diagnosis (Kuroiwa *et al.*, 1995).

The exact age at which a DNET arises is not clear, but many authorities argue for a dysembryoblastic origin, supported by the presence of multiple and distinct cell lineages in the tumour, the frequent association of cortical dysplasia and evidence of bone remodelling over more superficial lesions (Daumas-Duport *et al.*, 1988; Hirose *et al.*, 1994). By this reasoning, the age of onset of damage to the amygdala in patients with a DNET is thus in the embryonal or fetal periods.

A complementary, if more conservative method of establishing the developmental age of an amygdalar lesion is to adopt the age of onset of habitual seizures caused by the lesion. This method has been used in research into the effects of damage to mesial temporal lobe structures on memory and the perception of emotional expressions (Lespinet *et al.*, 2002; Meletti *et al.*, 2003). This approach has the advantage of reflecting the presence of a lesion that is clinically apparent, acting as an epileptogenic focus with adverse effects on the neurophysiological integrity of local neuronal populations. In this study, both approaches are employed: for the primary analyses, the early amygdala group is defined by the presence of a focal amygdala lesion (regardless of age of onset of seizures). In further exploratory analyses, the developmental age of the amygdalar lesion is taken more conservatively to be the age at which it became clinically apparent, acting as an epileptogenic focus.

Damage in adult life to the amygdala usually occurs as a result of a temporal lobectomy or amygdalo-hippocampectomy as part of surgical treatment of medically intractable epilepsy. In most of these cases, the amygdala will show pathological changes such as sclerosis. However, occasionally, a normal amygdala will have been excised, and such subjects effectively acquire damage to a normal amygdala in adult life. The age of onset of amygdala damage in such subjects is thus the age of the operative excision of the amygdala (and surrounding structures). As all these subjects typically have epilepsy and are on anticonvulsant medication, it is clearly important to have an appropriate clinical comparison group. We chose a group of subjects with epilepsy arising from similar focal pathologies affecting the temporal or parietal lobe which completely spared the amygdala.

We thus aimed to explore systematically the effects of early and late developmental damage to the amygdala on 'ToM.' We predicted that subjects with early amygdala lesions would be impaired on tests of ToM reasoning compared with both healthy and clinical comparison groups. In line with the earlier discussion, we also predicted that subjects who acquired damage to a normal amygdala in adult life would not show such impairments. We also examined the possibility that there may be an interaction between the content of the ToM task and the side of amygdala which mediates its processing. Specifically, on the basis of previous case reports, we predicted that subjects with lesion of the left amygdala would show greater impairment on ToM tasks which involved epistemic attributions and subjects with right-sided lesions would have greater impairment on affective state attributions.

Subjects and methods

Participants

All clinical subjects were recruited from the regional neuroscience centre at King's College Hospital, London. The early amygdala damage group all had lesions which centred on the amygdala with minimal extension. Neuroradiological differential diagnoses of the lesion were made by consultant neuroradiologists, and the clinical histories were reviewed by consultant neurosurgeons and neurologists to ensure they were compatible with the presence of an indolent non-progressive tumour of the amygdala, such as a DNET (Honavar *et al.*, 1999). For some analyses, the age of acquisition of the DNET was taken conservatively to be the age of onset of seizures which arise from the lesion. The late amygdala damage group had all received surgical treatment for their epilepsy with either an *en bloc* anterior temporal lobe resection. The normality of the excised amygdala was defined neuroradiologically as a preoperative volume of the amygdala falling within 1 SD of the mean volume of the amygdala measured in 66 neurologically intact subjects. Previous work has found that preoperative volumetric analysis of MRIs of the amygdala is sensitive to the presence of even minimal sclerosis (Hudson *et al.*, 1993; Lambert *et al.*, 2003). Additionally, the excised amygdala had to display no gross or microscopic abnormality on histological examination. The age of onset of damage to the amygdala in this group is the age at which the normal amygdala was surgically excised. The clinical comparison group had lesions which spared the amygdala (see Table 1 for details of all lesions). These lesions were of a similar nature to those of the subjects with early damage to the amygdala with a preponderance of DNETs. Healthy controls were recruited from a database of volunteers held locally with no history of neurological or psychiatric disorders.

Ethical approval for the study was given by the Research Ethics Committee at the South London Maudsley NHS Trust and King's Healthcare NHS Trust, and subjects gave consent obtained in accordance with the Declaration of Helsinki.

Neuroimaging

For volumetric analyses, a 3D inversion recovery prepared fast spoiled GRASS T1-MRI weighted data set was obtained in the coronal plane with 1.5 mm contiguous sections. The volume of the amygdala was measured using existing protocols (Watson *et al.*, 1992; Brierley *et al.*, 2002) and adjusted for intracranial volume in the preoperative scans of the subjects in the late acquired damage group. Two independent raters with high inter-rater reliability performed the volumetric analyses (intracranial content for the amygdala 0.95). MRIs from selected patients in each group are shown as Supplementary data available at *Brain* Online.

Tasks

Clinical groups completed the vocabulary, digit span, comprehension and similarities subscales for verbal intelligence quotient (IQ), and the block design and object assembly subscales for performance IQ (Wechsler, 1997*b*). An estimate of IQ was obtained from the National Adult Reading test for the neurologically intact control subjects (Nelson, 1982). Memory was assessed with the immediate and delayed logical memory test from the Wechsler Memory Scale—third version (Wechsler, 1997*a*). Executive function was assessed using the Hayling and Brixton tests (Burgess and Shallice, 1996*a*, *b*). The Hayling test provides a measure of the ability to inhibit a prepotent response as well as task initiation speed. The Brixton test is a rule detection and set shifting task.

Experimental tasks

False belief tasks

Examples of all tasks are given in the Supplementary data. The false belief tasks were adapted from vignettes designed by Baron-Cohen and colleagues with superficial changes made to make the content more suitable for adults (Baron-Cohen *et al.*, 1985; Baron-Cohen, 1989). Subjects must predict the actions of a character on the basis of the character's mistaken belief. Both first order ('Peter thinks that....) and second order tasks ('Susan thinks that Peter thinks....') incorporating control questions assessing comprehension and memory were included. Throughout all testing, subjects were read the vignettes and also held their own copies to minimize memory load. Throughout, overall scores are expressed as percentages to allow for comparison across tasks.

Happé's strange stories

In these vignettes, characters typically say something they do not mean literally and the participant is required both to demonstrate comprehension of the statement and explain the possible motivations underlying it. Stories on themes of lying, double bluff, being tactful and persuasion were included (with minor superficial alterations). In line with Happé and collaborators, we coded the responses as including a completely and explicitly correct mental state reference (scoring 2 points), a context-appropriate mental state which only implicitly correctly answered the question or a response which contained no references to mental states but purely physical terms (both scoring 1 point), or an incorrect response (scoring 0 points). These scores were then expressed as percentages. For details see Happé (1994) and Snowden *et al.* (2003).

Metaphor and irony

Several theorists argue that the understanding of metaphor can be achieved by grasping the intentions of the speaker; it thus requires a first order ToM. In contrast, the comprehension of an ironic statement requires the ability to appreciate the thought of the speaker and also the speaker's attitude towards that thought, i.e. have second order meta-representational abilities exemplified by a second order ToM. In each vignette, the chief protagonist makes both a metaphorical and an ironic comment and the participant is asked to interpret the intent of the protagonist. Responses were coded as correct or incorrect and converted to percentage scores. For details see Happé (1993).

Faux pas task

The *faux pas* task explicitly assesses various constituent components of theory of mind. In each of nine vignettes, person A unintentionally says something which will hurt the feelings of person B. Participants were then asked if someone in the story had said something awkward (detection of the *faux pas*), to identify who made the *faux pas* and to explain why s/he should not have made the comment (the epistemic attribution, 'he didn't realize

Table 1 *Details of lesion location and pathology*

Subject	Side	Lesion	Estimated age of amygdala damage (years)*	Pathology
Early amygdala damage group				
EA2§	L	Amygdala only	1	DNET
EA7	R	Amygdala only	21	DNET
EA3§	L	Amygdala only	11	DNET
EA4	L	Amygdala only	1	DNET
EA9	R	Amygdala only	1	DNET
EA10	R	Amygdala only	6	DNET
EA12	L	Amygdala only	18	DNET
EA14	R	Amygdala only	26	DNET
EA15	L	Amygdala only	24	DNET*
EA6	L	Amygdala extending to entorhinal cortex	20	DNET
EA11	L	Amygdala extending to lentiform nucleus	1	DNET
EA13	R	Amygdala extending to uncus	16	DNET
EA1§	L	Amygdala extending to temporal pole	18	DNET*
EA5	L	Amygdala extending to temporal pole	3	DNET*
EA8	R	Amygdala extending to temporal pole	12	DNET*
Late damage to a pre-operatively normal amygdala				
LA9	L	Anterior temporal lobectomy	18	Mild sclerosis of hippocampus*
LA2	R	Radiotherapy damage to ATL including anterior amygdala	35	Previous AVM in ATL
LA1	L	Anterior temporal lobectomy	39	Temporal DNET*
LA3	R	Anterior temporal lobectomy	31	Temporal epidermoid*
LA4	R	Anterior temporal lobectomy	20	None*
LA5	R	Anterior temporal lobectomy	26	Mild sclerosis of hippocampus*
LA6	R	Anterior temporal lobectomy	25	None*
LA7	R	Anterior temporal lobectomy	48	None*
LA8	R	Anterior temporal lobectomy	39	None*
LA10	L	Anterior temporal lobectomy	18	Parahippocampal DNET*
LA11	R	Anterior temporal lobectomy	44	Uncal cavernoma*
Clinical comparison group				
CC1§	L	Temporal pole (antero-inferior portion)	No damage to the amygdala	DNET*
CC2§	L	Parahippocampus	N/A	DNET
CC7	R	Parahippocampus	N/A	Cavernoma*
CC4	R	Parietal lobe	N/A	Cavernoma
CC11§	L	Parieto-occipital junction	N/A	DNET*
CC5	L	Temporo-parietal junction	N/A	DNET*
CC10	R	Insula	N/A	Surgical excision*
CC6	L	Parahippocampus	N/A	DNET*
CC8	L	Hippocampus	N/A	Dysplasia
CC12§	R	Temporal operculum	N/A	DNET
CC9	R	Anterior temporal lobe	N/A	Ganglioglioma
CC14	R	Temporo-parietal junction	N/A	Epidermoid
CC13	R	Occipital cortex	N/A	Cortical dysplasia
CC3	R	Anterior temporal lobe extending to frontal operculum	N/A	DNET*

For the 'early' damage group (DNET), a conservative method of dating the age of damage to the amygdala as the age of onset of seizures is used. For the 'late' amygdala group, the age of damage is the age of surgical excision of the previously normal amygdala. AVM = arteriovenous malformation; ATL = anterior temporal lobectomy; L = left; R = right; N/A = not applicable; *diagnosis confirmed by histology; §MRIs shown in Appendix 1.

he....'). Subjects are also asked about the emotional response of person B (the affective attribution, 'He would feel hurt...'). Finally, a question relating to story comprehension was asked. One point was given for: correct detection of the *faux pas* and the person who had made it, a correct epistemic attribution and a correct affective attribution, giving a maximum score of 27, which was then converted to an overall percentage score. For details see Stone *et al.* (1998)

'Conflicting belief and emotion' task

This is a novel task in which participants are given vignettes which concerned two protagonists A and B and centred on a social scenario, typically on themes of social exclusion or threat. In the vignette, A holds a true first order belief and B holds a false second order belief. Each belief is associated with an emotional state—in each scenario one of the emotional states has a positive valence and the other a negative valence (see Supplementary data). Participants

Table 2 *Demographic and neuropsychological characteristics*

	Early amygdala	Late amygdala	Clinical comparison group	Healthy comparison group	Significance
Sex (M : F)	7 : 8	7 : 4	6 : 8	17 : 21	$\chi^2(3) = 1.39$, $P = 0.71$
Age (years) mean (SD)	35 (13)	32 (12)	27 (7)	36 (11)	$F = 2.46$, $P = 0.07$
Age (years) of onset of epilepsy	12 (10)	17 (9)	17 (9)	–	$F = 0.85$, $P = 0.44$
Verbal IQ	98 (13)	96 (11)	94 (13)	112 (9)	$F = 12.4$, $P = 0.001$; EA***, LA***, CC*** < NCC
Performance IQ	102 (14)	98 (18)	101 (18)	111 (6)	$F = 4.5$, $P = 0.01$; LA* < NCC
Logical memory-scaled scores	7.4 (2.9)	8.3 (3.2)	8.0 (2.6)	11.4 (2.5)	$F = 11.7$, $P < 0.001$; EA***, LA***, CC** < NCC
Brixton	5.6 (1.7)	5.9 (1.6)	6.1 (1.8)	6.9 (1.0)	$F = 2.7$, $P = 0.052$
Hayling	5.6 (1.4)	5.0 (1.3)	5.4 (1.8)	7.1 (1.3)	$F = 9.1$, $P < 0.001$; EA***, LA***, CC** < NCC

EA = early amygdala damage; LA = late acquired amygdala damage; CC = clinical comparison group; NCC = healthy comparison group. Levels of significance: ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$. M = male; F = female.

are asked, in a random order, questions designed to assess their understanding of the two conflicting beliefs and conflicting emotional states. Control questions testing memory for the story and inference making are included. Answers given in response to the question concerning second order false belief were coded using the same method as in the Happé strange stories, with responses categorized as containing a full mental state, partial mental state or physical state response.

Effect of side of lesion and content of task.

To explore the hypothesis that left-sided amygdala lesions will more severely impair epistemic, and right-sided lesions affective ToM reasoning, scores on tests requiring epistemic attributions (epistemic components of *faux pas* and conflicting belief and emotion) and tests assessing affective inferences (affective attributions in the *faux pas* and conflicting beliefs and emotions task) were combined. An index of 'content specificity' was calculated by using the equation (total epistemic attributions – total affective attributions)/(total epistemic + total affective attributions). This index thus expressed the difference in performance arising from the content of the task, adjusted for a measure of overall accuracy.

Results

Demographic and neuropsychological measures

There were no significant differences on the basic neuropsychological measures between the clinical groups, who were, however, significantly impaired relative to healthy comparison subjects on most measures. Demographic variables were similar for all the groups. Although the age of onset of habitual seizures was lower in the early amygdala damage than the late amygdala damage group, this did not reach statistical significance (Table 2).

False belief tasks

No subject made errors on the first order false belief questions (Table 3).

Four subjects with early amygdala damage and one late amygdala subject made errors on the second order false belief task, although the group difference in total number of errors did not reach significance.

Happé's strange stories

There was a main effect of group in overall scores, and *post hoc* analyses with Tukey's HSD (honestly SD) test confirmed significant differences between the early amygdala damage group and the late amygdala, clinical and healthy comparison groups and between the clinical and healthy comparison groups (Fig. 1).

This arose largely as there was a group effect in the number of full mental state attributions made [$F(3,74) = 7.79$, $P < 0.001$]. *Post hoc* analyses showed that the early amygdala group made significantly fewer full accurate mental state attributions than the late amygdala group ($P = 0.01$), the clinical comparison ($P = 0.045$) and healthy comparison groups ($P < 0.001$). For results, see Table 3.

Metaphor and irony

The results (Table 3) were highly skewed as subjects in late amygdala damage and comparison groups made no errors. There was no effect of group on comprehension of metaphor. A Kruskal–Wallis test demonstrated a significant group difference in the comprehension of irony, with pairwise comparisons showing the difference to be in the early amygdala relative to healthy comparison group ($Z = -3.1$, $P = 0.001$) and trend for an impairment relative to the late amygdala group ($Z = -1.89$, $P = 0.06$).

Faux pas *task*

There were no group differences in the scores on control questions (with all groups displaying near perfect scores). There was a significant effect of group on the total number of

Table 3 *Results for each group on ToM tests*

	Early amygdala (15)	Late amygdala (11)	Clinical comparison group (14)	Healthy comparison group (38)	ANOVA (and *post hoc* Tukey's HSD) or Kruskal–Wallis (and pairwise Mann–Whitney)
False belief					
Number of subjects making errors	4	1	1	2	χ^2 =5.7, P = 0.13
Happé strange stories, metaphor and irony					
Strange stories mean (SD); correct/incorrect	78 (13)	90 (7)	90 (12)	96 (6)	$F(3,74)$ = 14.6, P < 0.001, EA <**LA, **CC, ***NCC, CC < *NCC
Metaphor; median (quartiles)	100 (100–100)	100	100	100	$\chi^2(3)$ = 2.21, P = 0.52
Irony; median (quartiles)	100 (70–100)	100 (100–100)	100	100	$\chi^2(3)$ = 10.9, P = 0.012, EA < ***NCC
Faux pas					
Detection; median (quartiles)	100 (87–100)	100 (78–100)	100 (97–100)	100	$\chi^2(3)$ = 10.8, P = 0.01, EA < ***NCC, LA < **NCC
Affective attributions	100 (64–100)	100 (75–100)	100 (97–100)	100 (90–100)	χ^2 = 5.3, P = 0.16
Epistemic attributions	89 (70–100)	100 (65–100)	94 (86–100)	100	χ^2 = 16.9, P = 0.001, EA < *CC, ***NCC, LA < *NCC
Total score	89 (73–100)	100 (74–100)	98 (92–100)	100	χ^2 = 7.39, P = 0.06, EA < CC (P = 0.06), EA < **NCC
Conflicting beliefs and emotions					
Belief; true first order; median (quartiles)	100 (96–100)	100 (95–100)	100 (96–100)	100	$\chi^{2(3)}$ = 4.2, P = 0.24
Belief; false second order	93 (67–100)	100 (87–100)	93 (86–100)	100	χ^2 = 11.9, P = 0.01, **EA <NCC, *LA < NCC, *CC < NCC
Emotion; first order	87 (75–100)	87 (80–100)	100 (86–100)	100	χ^2 = 9.0, P = 0.03, EA <*CC, **NCC
Emotion; second order	85 (62–87)	85 (74–90)	100 (86–100)	100 (87–100)	χ^2 = 16.4, P = 0.001, EA < **CC, ***NCC

Level of significance of *post hoc* comparisons: *P < 0.05, **P < 0.01, ***P < 0.001. EA = early amygdala damage; LA = late amygdala damage; CC = clinical comparison group; NCC = healthy comparison group.

correct detections and epistemic attributions, but not in affective attributions. Errors in the epistemic attributions all involved assuming that the *faux pas* had been made intentionally with the aim of upsetting the other protagonist in the vignette. There was a significant group difference in overall performance, with pairwise Mann–Whitney comparisons showing that the early amygdala group were significantly impaired relative to the healthy comparison group (Z = –2.7, P = 0.007) and there was a near significant impairment relative to the clinical comparison group (Z = –1.84, P = 0.066).

Conflicting beliefs and emotions' task

One subject in the late amygdala damage and one in the early amygdala group failed to complete the test. There was no significant difference between the groups in the memory and inference questions. Performance on the first order true belief component was nearly at ceiling in all groups, and a Kruskal–Wallis test showed no effect of group (see Table 3). In the attribution of second order false beliefs, there was a significant difference between the groups in overall number of incorrect responses [$F(2,72)$ = 4.3, P = 0.008], with the early amygdala group making more such errors than the healthy comparison group (P = 0.01). There was a significant

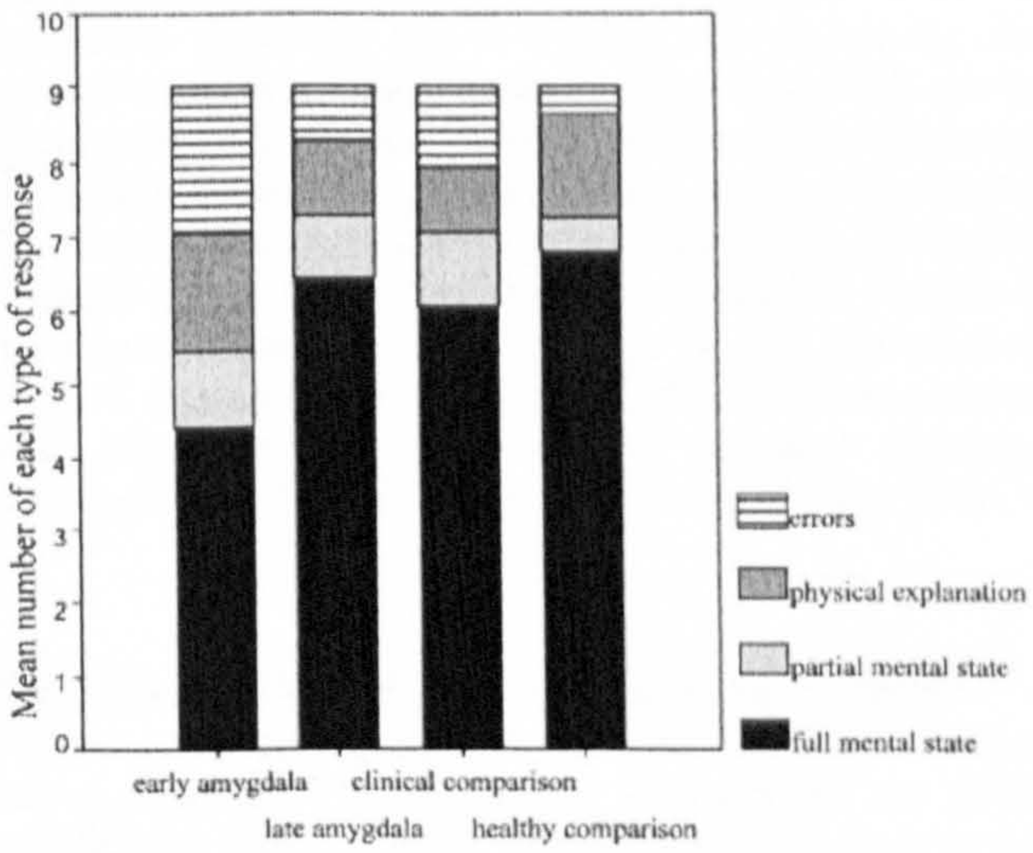

Fig. 1 Type of response in Happé's strange stories (a total of nine stories were used and the diagram illustrates the number of each type of response).

group difference in the number of correct responses which contained a full mental state reference [$F(3,72)$ = 5.4, P = 0.004] and physical state references [$F(93,72)$ = 3.7, P = 0.01]. *Post hoc* Tukey's HSD test showed that the early

Table 4 *Mean (SD) cumulative score on all ToM tests for each group*

	Early amygdala mean 81.4 (10.3)	Late amygdala mean 89.2 (7.9)	Clinical comparison mean 90.4 (8.1)	Healthy comparison mean 95.9 (4.7)
Early amygdala	–	0.79	0.89	1.55
Late amygdala	–	–	0.17	1.09
Clinical comparison	–	–	–	0.87

Effect sizes between each group are expressed as Cohen's d.

Table 5 *Pearson correlations between ToM tests (overall score) and IQ, logical memory and executive function*

Group	VIQ	PIQ	Logical memory	Brixton	Haylings
Early amygdala	0.43	0.21	–0.04	0.35	0.56
Late amygdala	0.35	0.29	0.12	0.57	0.42
Clinical controls	0.17	0.46*	0.50*	0.22	0.19
Healthy controls	0.27	0.28	0.32*	0.16	0.27

PIQ = performance IQ; VIQ = verbal IQ. *Significant at $P < 0.05$.

amygdala group gave fewer mental state responses ($P = 0.004$) and more attributions containing a physical state reference ($P = 0.049$) than the healthy comparison group. There was no effect of group on the number of partially correct mental state attributions [$F(3,72) = 0.01$, $P = 0.96$).

All but four subjects made more errors in emotional than belief attributions. There was a significant group difference in the number of correct emotional attributions associated with both first and second order beliefs. *Post hoc* analyses showed that the early amygdala damage group made more errors in providing an emotion which was congruent with the belief state of the characters relative to both clinical ($Z = -2.7$, $P = 0.006$) and healthy comparison groups ($Z = -3.0$, $P = 0.001$).

Overall performance

A cumulative score reflecting in equal measure the scores on the four tests was calculated (Table 4).

There was a significant group difference [$F(3,74) = 15.4$, $P < 0.001$] with impairment in the early amygdala damage group relative to all the other groups (late amygdala damage group $P = 0.04$, clinical control group $P = 0.006$, and healthy control group $P < 0.001$, Bonferroni corrected contrasts). The late amygdala damage group were significantly impaired relative to the healthy comparison group only ($P = 0.05$). Effect sizes were also calculated, using Cohen's d, a statistical power analysis quantifying the size of the difference between groups (Cohen, 1992). The index is interpreted as indicating a small between-group difference for d = 0.20, medium for d = 0.50 and large for d > 0.8. All clinical groups were substantially impaired relative to the healthy comparison group. The early amygdala group showed a large (d = 0.92), and the late amygdala group showed a small (d = 0.21) difference relative to the clinical comparison group.

The relationship with general intelligence, memory and executive function

There were modest positive correlations within each group between these variables and the overall measure of performance on ToM tests, but no significant interactions between these covariates and the measure of overall performance in each group. We thus reanalysed the data with these measures as covariates

The significant difference between the early amygdala damage group and all other groups held in pairwise comparisons between the individual groups (with a Bonferroni correction and $P < 0.05$) after co-varying for executive function, logical memory and general intelligence. The significant difference between the late amygdala damage and healthy comparison groups similarly survived co-varying for these measures (pairwise comparison with Bonferroni correction, $P < 0.01$). However, the significant difference between the late amygdala damage group and clinical controls in overall performance in ToM tests did not remain after adjustment for differences in executive function, memory and IQ between the groups. For results see Table 5.

The effect side and size of lesion and gender

For the cumulative score, subjects with right-sided lesions had a mean score of 86.7 (SD 11) which did not differ significantly from the mean score of 86.7 (SD 10.4) or the score of the subjects with left-sided lesions [$t(38) = 0.02$, $P = 0.98$]. For the early amygdala damage group, there was also no significant difference [$t(13) = 0.14$, $P = 0.88$] between those with right- (mean score 82, SD 9) and left-sided damage (mean score 81, SD 12). There was no significant difference between the subgroup of early amygdala damage subjects whose lesions were confined to the amygdala (nine subjects) and those with lesions which had some extension into

Table 6 *Results in the overall performance on ToM tests by gender*

	Early amygdala	Late amygdala	Clinical comparison group	Healthy comparison group
Male; median (quartiles)	79 (75–85)	90 (75–96)	94 (83–99)	96 (94–98)
Female; median score (quartiles)	82 (76–91)	91 (85–95)	90 (84–96)	98 (94–99)
Mann–Whitney *U* test	$Z = -0.69$, $P = 0.49$	$Z = -0.37$, $P = 0.71$	$Z = 0.9$, $P = 0.36$	$Z = -1.02$, $P = 0.3$

adjacent structures (six subjects) on any of the ToM measures [Happé $t(13) = 1.08$, $P = 0.27$; *faux pas* $t(13) = 1.66$, $P = 0.12$; belief and emotion $t(13) = 0.76$, $P = 0.46$; false belief and deception $t(13) = 0.15$, $P = 0.87$].

An index of content specificity was calculated to give a measure of the relative performance on epistemic versus affective ToM reasoning. The side and location of damage (24 amygdala damage and 14 non-amygdala damage) were then entered into a 2 × 2 analysis of variance (ANOVA) with the index as the dependent variable. There was no main effect of side [$F(1,34) = 1.18$, $P = 0.28$] or location of damage [$F(1,34) = 1.4$, $P = 0.23$] and no interaction [$F(1,34) = 1.1$, $P = 0.30$].

As can be seen from Table 6, there were no significant gender differences within each group, although in the early and late amygdala damage group and the healthy control group, females tended to perform slightly better. Collapsing the results for the cumulative index across all groups, females had a marginally higher score than males (female mean 91.7, SD 7.1; male mean 90.7, SD 10; $t = -0.53$, $P = 0.60$).

Relationship with the age of onset of damage to the amygdala

As discussed earlier, the age of damage for the early amygdala group can be taken to be the age of onset of seizures which arise from the lesion. The age of damage to the amygdala in the late onset group is the age at which the patient underwent its surgical excision. As would be expected, the age of damage to the amygdala in the 'early damage group' was in childhood (12 ± 9 years; mean ± SD) and in the late amygdala damage group in adult life (31 ± 10 years). This difference was highly significant ($t = 4.8$, $P < 0.001$). There was a significant positive correlation between the age of onset of amygdala damage and the overall score (Spearman's rho = 0.64, $P < 0.001$). Figure 2 illustrates this correlation, with the overall score expressed as number of standard deviations from the mean of the healthy comparison group.

All patients with a DNET who had an onset of epilepsy in childhood (<16 years) fell at least 2 SDs below the mean of the healthy comparison group. Four of the six patients who had a DNET associated with adult onset of seizures were less impaired (falling within 2 SDs of the healthy comparison group). Turning to the late amygdala damage group, only two of the 11 subjects scored 2 SDs below the healthy comparison group. The age of onset of habitual seizures was not related to the degree of impairment in ToM reasoning in the late amygdala and clinical comparison groups (Spearman's rho = 0.28, $P = 0.39$ for the late amygdala damage group, and Spearman's rho = 0.31, $P = 0.28$ for the clinical controls). Thus it is unlikely that an early age of onset of seizures *per se*, regardless of the location of the epilpetogenic focus, leads to deficits in ToM reasoning.

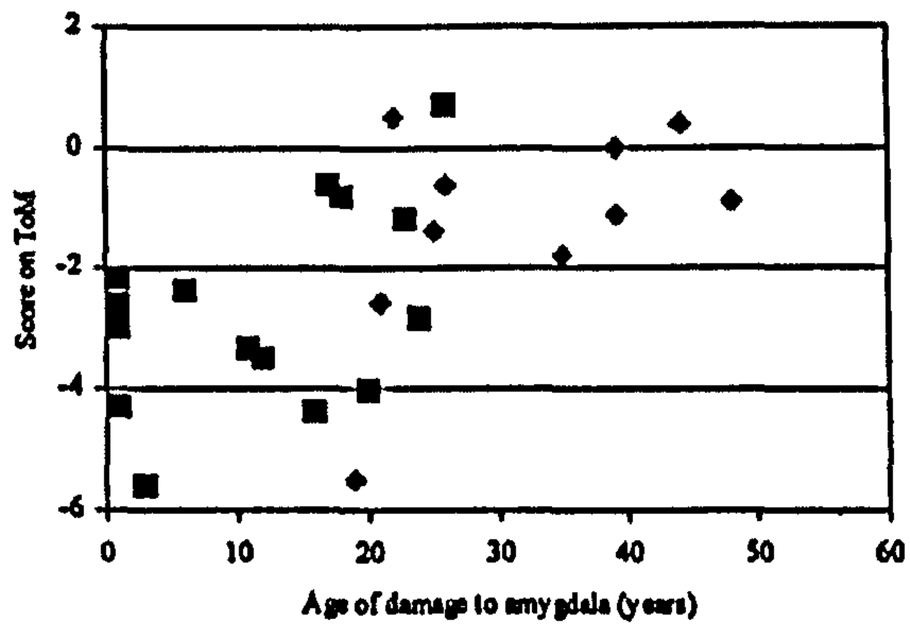

Fig. 2 Relationship between the age of damage to the amygdala and overall score on the ToM battery (scores expressed as standard deviations from mean score of healthy comparison group). Filled black squares = early amygdala damage group (DNETs); filled grey diamonds = late amygdala damage group (surgical excision).

Discussion

Key findings

The study demonstrated deficits in advanced tests of reasoning about the mental states of others among subjects with lesions of the amygdala arising early in development, particularly if associated with childhood onset of seizures. In contrast, subjects with lesions of the amygdala acquired in adult life showed no significant impairment in ToM tasks relative to a clinical comparison group of subjects with lesions which spared the amygdala. This pattern of deficits held after co-varying measures of general intelligence, executive function and verbal memory. There was no effect of side of damage or gender on overall performance. There was also no evidence of an interaction between the side of amygdala damage and impairment on specific types of mental state attribution (epistemic versus affective).

In the primary analyses, the developmental stage of amygdala damage was defined pathologically; early amygdala damage subjects had a presumed DNET and late amygdala damage subjects had a histologically normal amygdala excised in adulthood. Given the uncertainly about the exact age at which DNETs arise, we include a complementary method of dating the age of the amygdala lesions, i.e. taking the age of onset of the lesion to be the age of onset of associated epilepsy. Adopting this method, all subjects with amygdala lesions associated with a childhood onset of seizures (<16 years) had impaired ToM reasoning compared with healthy subjects. In contrast, only two subjects with damage to the amygdala which arose in adult life due to surgery showed marked ToM impairments. This raises the possibility of a sensitive period in development of ToM reasoning which extends to late childhood, during which damage to the amygdala leads to impairments, particularly if the damage is so severe as to be clinically and neurophysiologically apparent. Research into healthy children suggests that the ability to perform the *faux pas* task is acquired in late childhood (between the ages of 7 and 11 years), several years after children reliably pass first and second order false belief ToM tests (Baron-Cohen *et al.*, 1999*a*; Wellman *et al.*, 2001). Deficits in the early amygdala damage group are only apparent in the developmentally advanced tests of ToM such as the *faux pas*, implying that such damage is associated with a degree of developmental delay, rather than developmental arrest.

We can speculate about the possible cognitive origins of this delay. The amygdala appears to be a pivotal structure in supporting some of the earliest precursors of ToM reasoning. Lesion and fMRI studies both suggest that it plays a critical role in monitoring the direction of eye gaze necessary to engage in shared attention and detecting the emotional states of others on the basis of their appearance (Baron-Cohen *et al.*, 1999*b*; Kawashima *et al.*, 1999; Morris *et al.*, 2002; Zald, 2003). By disrupting such precursors of ToM reasoning, early damage to the amygdala may thus slow the trajectory of the development of ToM, in many cases preventing subjects reaching the most advanced stages of the skill. This may explain the pattern of deficits found in the early amygdala damage group of generally intact, but not perfect, basic ToM function, and impaired, qualitatively anomalous performance on the more complex tasks of ToM such as the *faux pas* and comprehension of irony. This explanation links the role of the amygdala in emotional perception with a role in ToM reasoning.

Early damage to the amygdala has been linked explicitly to the later development of autism, which arguably has impaired ToM reasoning as its core neurocognitive deficit. It is interesting that the quality of the correct responses given by the subjects with early amygdala damage is reminiscent of those given by people who have autism (Happé, 1994; Jolliffe and Baron-Cohen, 1999). For example, in Happé's strange stories and the novel conflicting belief and emotions tasks, the subjects with early amygdala lesions tended to give fewer correct answers couched in explicitly correct mental state references. This is suggestive of impairment in spontaneously and automatically 'mentalizing' when faced with the task of interpreting the actions of other agents. Similarly, participants with early amygdala damage frequently made inappropriate affective attributions in the conflicting belief and emotion test, even when they made the correct epistemic attributions. This is reminiscent of the finding by Baron-Cohen (1991) that subjects with autism find the comprehension of emotional states particularly difficult when they are associated with belief states (rather than, for example, those evoked by a certain situation). Given the similarities between these responses and those given by subjects with autism and Asperger's syndrome to similar stories, we would interpret such answers as reflecting an inability to reason accurately about the mental states of others. Thus, the impairments in ToM reasoning are qualitatively similar to those often reported in autism and Asperger's, and as such are consistent with the idea that the amygdala plays a role in the aetiology of these neurodevelopmental disorders.

There are several possible interpretations of the lack of deficits in the late amygdala damage group. First, it could be argued that the amygdala may be necessary for the performance of ToM reasoning and that just one intact amygdala is sufficient for this processing. There are several instances of functional reduplication within the brain whereby the loss of one structure is readily compensated for by the presence of its homologue. If this were the case, then deficits in ToM reasoning would be present in subjects with late acquired damage only if both amygdalae were affected, such as that found in subjects described by Stone *et al.* (2003), all of whom have some impairment in ToM reasoning tasks. This position would also explain the functional imaging reports of amygdala activation during putative ToM reasoning tasks. However, these lesion and functional imaging studies are open to criticism. First, two of the bilateral subjects (S.E. and D.R.) in the study of Stone *et al.* (2003) had damage to regions extending beyond the amygdala which may have contributed to the impairments in ToM tasks. One of the subjects (D.R.) had marked impairments in executive function which alone could have led to failure on many of the tasks, and the subject may also have had early developmental damage to one amygdala. Turning to the functional imaging studies, Frith and Frith (2003) have noted that the tasks which report amygdala activation use stimuli such as the human face and eye region, which may recruit the amygdala even in the absence of a clear ToM component. It is debatable the extent to which the simple attribution of a mental state to another person on the basis of their appearance is truly a 'ToM' activity, which some argue must entail a meta-representational component. None of the tasks which we employed which more clearly assess ToM reasoning has demonstrated amygdala activation during fMRI. Although the evidence from our study cannot rule out the possibility of an 'on-line' role for the amygdala, we feel it weakens the plausibility of this position. In other domains of social cognition such as moral reasoning, a similar relationship between impairments

Table 7 *Effect sizes (Cohen's d) of the difference between clinical groups and relevant comparison groups reported in different studies using Happe's strange stories*

Study	Clinical group	Comparison group	Cohen's d
Current study	Early amygdala	Healthy subjects	1.55
	Early amygdala	Clinical comparison	0.89
Happe (1994)	Subjects with high functioning autism*	Age-matched healthy subjects	1.23
	Subjects with autism who failed basic ToM tests	Age-matched healthy subjects	2.25
Jolliffe and Baron-Cohen (1999)	Subjects with high functioning autism	Age-matched healthy subjects	1.41
	Subjects with Asperger's syndrome	Age-matched healthy subjects	1.24
Happe *et al.* (1999)	Right hemisphere cerebrovascular accident	Age-matched healthy subjects	1.35

*High functioning autism refers to the ability to pass first and second order false belief tasks.

and the age of acquisition of a lesion has been reported. A comparison of the effects of early and late acquisition of lesions to the prefrontal cortex found more pervasive impairments in moral reasoning among subjects with early compared with late prefrontal cortex damage (Anderson *et al.*, 1999).

Several important cautions must be considered in this study. First, the impairment demonstrated by the early amygdala damage group might not be considered severe: the majority of subjects passed the standard first and second false belief ToM tests and were mostly intact in the detection of irony (which is in essence a test of second order ToM reasoning). Deficits were only apparent in the more advanced tests of ToM, and even in these tests the deficits in absolute terms were not great. It would therefore be important to place these impairments in the context of other groups who are also thought to exhibit ToM deficits. This is limited by the lack of a standardized battery of ToM tests, but some comparisons are possible from several studies which have used Happé's strange stories (Table 7).

On this test of advanced ToM processing, the deficits in the early amygdala group relative to a healthy comparison group are of a similar magnitude (reflected in a similar large effect size) to those shown by subjects with high functioning autism and Asperger's syndrome and subjects with extensive right hemisphere damage due to strokes. In the *faux pas* test, a direct comparison is possible with Stone's original study (Stone *et al.*, 1998). Patients with orbitofrontal damage had an estimated median score of 86% (interquartile range 76–96%), compared with performance at or near ceiling for subjects with dorsolateral prefrontal cortex lesions and healthy comparison subjects. These scores are similar to the median score of the early amygdala damage group of 89% (interquartile range 73–100%). Studies with subjects with autism and the frontal variant of fronto-temporal dementia are suggestive that the deficits in these groups on the *faux pas* test are more severe, but direct comparisons are difficult due to methodological differences (Baron-Cohen *et al.*, 1999*a*; Gregory *et al.*, 2002). These findings suggest that the early amygdala group have impairments in the advanced tests of ToM which are comparable with those of subjects with high functioning autism and Asperger's syndrome and those with lesions of other candidate components of the ToM neural circuitry.

Equally, the impairments in the subjects with early amygdala DNETs are not as severe as those found among most people who have autism, emphasizing the fact that we view early amygdala damage as only one of the contributors to a delay in the development of ToM reasoning.

A second important caveat is the presence of almost entirely normal ToM function in some of the subjects in the early amygdala group. Why were these subjects unimpaired? First, there is the possibility of a type 1 error, although the probability of this is low given the effect sizes reported. Secondly, the presence of intact performance in the face of amygdala damage raises the possibility that the amygdala may not be a core component of the development of ToM reasoning and may provide instead domain general support for ToM reasoning. By this reasoning, compensation for early damage to the amygdala may occur more readily as it is not a core component of ToM reasoning, and thus subjects with amygdala damage may not always demonstrate clear ToM impairments. If this were so, deficits would only be evident in tests which relied on the domain general functions of the amygdala (e.g. its role in memory for emotionally salient material used in some of the stories). While this is not excluded by our study, it is unlikely as the impairment of the early amygdala damage group relative to the other groups held after co-varying for a wide range of measures of general cognitive function. However, the case for a core contribution of the amygdala would be strengthened by the demonstration of deficits on a wider battery of tests, less reliant on verbal processing and comprehension than those used in the current study.

Finally, it is notable that all the unimpaired subjects with amygdala lesions had an adult onset of epilepsy (see Fig. 2). This may reflect the presence of a lesion which is less disruptive to amygdalar neuronal integrity leading both to a later age of onset of epilepsy and less impairment in the development of ToM. This is reminiscent of Jackson's hypothesis that a discharging or epileptogenic focal lesion may inhibit neuronal reorganization and compensation more than focal lesions which are 'non-discharging' (Jackson, 1931). Thus patients who have a clinically silent DNET

throughout early childhood may have been better able to compensate for the presence of an early focal lesion of the amygdala. We would, however, predict that such compensation may often not be complete, which would account for the deficits found in subjects with early amygdala lesions who have an adult onset of seizures. Additionally, we might expect that on more subtle measures of ToM processing such as reaction times or the quality of responses, differences may be apparent. As the age of onset of habitual seizures was not significantly correlated with the degree of impairment in ToM reasoning in the late amygdala and clinical comparison groups (whose epileptogenic lesions lie outside the amygdala), it is unlikely that an early age of onset of seizures *per se*, regardless of the location of the epileptogenic focus, accounts for the deficits in ToM reasoning.

The role of gender and other brain regions in ToM reasoning

Although the focus of the study was on the amygdala, some participants had damage to other structures which are held to mediate ToM reasoning, such as the temporal poles which are activated in fMRI studies tapping this domain (Frith and Frith, 2003). However, as can be seen from the individual results in Table 3, the subjects with early developmental, combined amygdala and temporal pole damage showed a range of scores spanning from the most impaired individual to subjects performing at average levels for the amygdala damage group. Subjects who acquired temporal pole damage as part of a temporal lobectomy were unimpaired compared with clinical controls. The left temporo-parietal junction recently has been isolated as another key region in ToM reasoning (Saxe and Kanwisher, 2003). Only one subject in this study had a lesion in this region (a DNET) and she made relatively few errors on the tasks, performing at the mean level for the clinical control group. Future work will examine more systematically the effects of lesions in these specific areas.

There were no significant gender differences within or across groups. This was a surprising finding as we might have expected males to compensate less readily for amygdala damage given the male predominance in developmental disorders with ToM impairments as a core feature.

Limitations of the study

A major potential drawback of this study is the difference in extent of extra-amygdala damage in the early onset and late onset groups, with the latter group generally having more extensive involvement of other anterior temporal lobe structures. However, if the greater volume of extra-amygdala tissue damage is functionally important, then we would expect those with most damage to be most impaired, which was not the case.

We did not include a control condition of stories which had a non-mental state content, which may help in excluding the possibility that impairment arises from factors unrelated to ToM reasoning such as the ability to form an integrated narrative from each vignette. However, the lack of a significant correlation between measures of general intellectual ability, executive function and ToM performance and the intact performance on the comprehension and inference conditions in the tests makes an explanation in these terms unlikely. Additionally, the vignettes for assessing the comprehension of irony and metaphor were structurally identical, yet deficits were only present in the interpretation of irony, which relies on intact ToM reasoning.

Conclusion

In conclusion, we found that lesions of the amygdala which arise early in development and act as epileptogenic foci in childhood were associated with deficits in ToM reasoning. Subjects who sustained surgical damage to a previously normal amygdala in adult life were intact in most tests of ToM relative to a clinical comparison group. These impairments cannot be reduced to executive dysfunction, which was not marked in the subjects with amygdala lesions and which did correlate strongly with overall performance. Although the findings were statistically robust and large effect sizes were observed, a minority of subjects had essentially normal ToM reasoning in the face of an amygdala DNET. All such subjects had an adult onset of epilepsy, perhaps reflecting a less aggressive amygdala lesion which may have also been less disruptive to the development of ToM reasoning. However, the presence of these intact subjects emphasizes the need for replication of these findings using complementary measures of ToM reasoning. The study provides initial evidence compatible with the postulation of the amygdala as part of the neural system which supports the development of ToM reasoning.

Supplementary data

Supplementary data are available at *Brain* Online.

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Measuring empathy: reliability and validity of the Empathy Quotient

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ABSTRACT

Background. Empathy plays a key role in social understanding, but its empirical measurement has proved difficult. The Empathy Quotient (EQ) is a self-report scale designed to do just that. This series of four studies examined the reliability and validity of the EQ and determined its factor structure.

Method. In Study 1, 53 people completed the EQ, Social Desirability Scale (SDS) and a non-verbal mental state inference test, the Eyes Task. In Study 2, a principal components analysis (PCA) was conducted on data from 110 healthy individuals and 62 people reporting depersonalisation (DPD). Approximately 1 year later, Study 3, involved the re-administration of the EQ ($n=24$) along with the Interpersonal Reactivity Index (IRI; $n=28$). In the last study, the EQ scores of those with DPD, a condition that includes a subjective lack of empathy, were examined in depth.

Results. An association was found between the Eyes task and EQ, and only three EQ items correlated with the SDS. PCA revealed three factors: (1) 'cognitive empathy'; (2) 'emotional reactivity', and (3) 'social skills'. Test–retest reliability was good and moderate associations were found between the EQ and IRI subscales, suggesting concurrent validity. People with DPD did not show a global empathy deficit, but reported less social competence.

Conclusions. The EQ is a valid, reliable scale and the different subscales may have clinical applications.

INTRODUCTION

There are several definitions of empathy reflecting its multidimensional nature. Social psychologists have conceptualized empathy as having two main strands (1) cognitive empathy – 'the intellectual/imaginative apprehension of another's mental state' and (2) emotional empathy – 'an emotional response to ... emotional responses of others'. Recently, in the literature, emotional empathy has also been labelled 'affective' empathy. The literature on 'theory of mind' (or the ability to think about the contents of other minds) overlaps with cognitive empathy and the terms are used interchangeably here.

For an emotional response to count as 'affective empathy' it has to be appropriate to the observed mental state. Emotional responses to others' mental states can be classified as: (1) parallel – the response matches that of the target, for instance, feeling fear at another's fright, and (2) reactive – involves going beyond a simple matching of affect – such as sympathy or compassion (Davis, 1994). However, some emotional responses are not considered truly empathic, i.e. happiness at another's misfortune or, less obviously, 'personal distress' (Davis, 1980; Eisenberg *et al.* 1987). The latter occurs when someone has a self-orientated state of 'personal distress' in response to another's

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negative state (Batson *et al.* 1987). What distinguishes this from an empathic response is that it is self- rather than other-orientated.

Several scales have been developed to measure empathy but each has important weaknesses. The Questionnaire Measure of Emotional Empathy (Mehrabian & Epstein, 1972) was designed to tap emotional empathy. However, with hindsight, the authors suggest it may measure general emotional arousability instead (Mehrabian *et al.* 1988). Items on a newer version – the Balanced Emotional Empathy Scale (Mehrabian, 2000) – measure, more specifically, reactions to others' mental states, but unfortunately, it is still not clear that they tap emotional empathy alone, e.g. 'I cannot easily empathise with the hopes and aspirations of strangers/I easily get carried away by the lyrics of a love song'. A questionnaire measuring cognitive empathy (Hogan, 1969) was also developed in the 1960s; however, a factor analysis suggested it may actually tap social self-confidence, even temperedness, sensitivity and non-conformity (Johnson *et al.* 1983). Critics also argue that it measures simply social skills rather than empathy *per se* (Davis, 1994).

The Interpersonal Reactivity Scale (Davis, 1980) adds further dimensions to the measurement of empathy. It includes subscales that measure perspective-taking, in line with traditional definitions of cognitive empathy, empathic concern which specifically addresses the capacity of the respondent for warm, concerned, compassionate feelings for others, fantasy items – which measure a tendency to identify with fictional characters and personal distress which is designed to tap the occurrence of self-orientated responses to others' negative experiences. The author describes the questionnaire as tapping four separate aspects of empathy but it is unclear whether the fantasy subscale taps pure empathy (Baron-Cohen & Wheelwright, in press) – and personal distress, despite being important, is not empathy in itself.

The EQ (Baron-Cohen & Wheelwright, in press) (see website for Appendix 1) is the most recent addition, and unlike previous scales it was explicitly designed to have a clinical application and be sensitive to a lack of empathy as a feature of psychopathology. Several groups have been hypothesised as having problems employing 'empathy'. Most obvious, are those diagnosed with autistic spectrum disorders and people who display signs of psychopathy (Blair, 1995). More recently, other groups have been suggested, such as those who report depersonalisation (Senior *et al.* 2001; Baker *et al.* 2003), who frequently complain of a subjective deficit in empathising.

The EQ was validated on 197 healthy control volunteers and 90 people with Asperger's Syndrome and High-functioning Autism (AS/HFA) and age and sex matched controls (a sex ratio of 2·6:1 m:f was found). It was shown to distinguish reliably between the clinical and control groups. The authors also found sex differences in the control group with women scoring significantly higher. In addition, the EQ was found to have high test–retest reliability over a period of 12 months. Baron-Cohen *et al.* (2003) replicated the female superiority on the EQ and showed once again that it distinguished between those with AS/HFA and controls.

The aim of this paper was to examine further the validity and reliability of the EQ across samples. Test–retest reliability was re-examined, and the association between the EQ and a well-validated measure of 'social desirability' (Crowne & Marlowe, 1960) was explored. This was included to address a general problem with self-report measures, that is that people may respond according to how they would like to appear, i.e. highly 'empathic'. The association between the EQ and the Eyes task (Baron-Cohen *et al.* 2001) was also considered as a means of assessing construct validity. Next, an exploratory factor analysis was performed in order to explore the various components of empathy. As a further check on concurrent validity, the relationship between the EQ and the Interpersonal Reactivity Index (IRI; Davis, 1980) was then examined. Lastly, the EQ scores of people with DPD were considered in depth.

Study 1

Participants

There were 53 volunteers [28 (52·8%) women and 25 (47·2) men] with a mean age of 32·5 years (±10·9). Approximately, 50% of this group were recruited from mental health professionals at the Institute of Psychiatry (40% of men and

60% of women). The remainder were recruited from non-academic/clinical staff and through advertisements in the local area.

Procedure

All measures were completed in a quiet room as part of a wider testing session. Participants were given the EQ (Baron-Cohen & Wheelwright, in press) self-report measure of empathy. Responses are given on a 4-point scale ranging from 'strongly agree' to 'strongly disagree'. Approximately half the items are reversed. Participants received 0 for a 'non-empathic' response, whatever the magnitude, and 1 or 2 for an 'empathic response' depending on the strength of the reply. There are 60 items including 20 filler items – and so the total score is out of 80. Missing values on the EQ, resulting from a double endorsement or no endorsement, were substituted with the group mean rounded to the nearest whole number.

Participants were also given the Social Desirability Scale (SDS; Crowne & Marlowe, 1960) which taps people's tendency to respond to items in a socially desirable way. One point is allocated for each item endorsed, resulting in scores ranging from 1 to 33 with a high score indicating that the respondents are prone to give answers which show themselves in a good light, i.e. 'I sometimes feel resentful when I don't get my own way'.

The Eyes test (Baron-Cohen *et al.* 2001; Shaw *et al.* 2003) was also administered. This measures peoples' ability to decipher a mental state from pictures of the eyes alone and according to the authors, is an advanced measure of mind-reading or in our terminology 'cognitive empathy'. This test has been shown to distinguish reliably between people with AS/HFA and healthy individuals. One point is allocated for each correct answer with a final score out of 36.

Lastly, participants completed the National Adult Reading Test (Nelson, 1982). Participants read 50 irregular sounding words (i.e. ache), which yields an estimate of IQ.

Results

Mean total EQ scores for both men and women can be found in Table 1. These are similar to those found in the original study (Baron-Cohen & Wheelwright, in press), i.e. males 41·8 (±11·2) and females 47·2 (±10·2). Sex differences were also found ($t=-3{\cdot}5$, df=51, $p=0{\cdot}001$). The data were normally distributed [slightly negative skew (−0·190) and kurtosis of less than 1 (−0·717)].

Table 1. *Mean and s.d. scores on the EQ*

		Total score on the EQ			
	n	Mean	s.d.	Min	Max
Male	25	41·3	10·1	22	58
Female	28	50·6	9·2	30	66
Group total	53	46·2	10·6	22	66

Each item on the EQ was entered into a Pearson's Product Moment Correlation analysis along with the total score on the SDS. A positive correlation above 0·3 was taken as an indicator of socially desirable responding. Items 11, 18, 27, 34 and 37 of the EQ, all correlated significantly with total SDS score but item 27 correlated below 0·3, and item 37 had a negative rather than positive relationship. Items 11, 18 and 34 were therefore dropped from subsequent analyses.

The mean score on the Eyes test was 27·6 (±4) which is very similar to the normative data (general population 26·2/students 28). These data were then correlated with total EQ score and a modest positive relationship was found ($n=48$, $r=0{\cdot}294$, $p=0{\cdot}033$).

The estimated IQ score from the NART for this group was 120·48 (±4·7) which is above the average range. As both the Eyes test and EQ have verbal components, a correlational analysis was run to examine the association between verbal IQ, as estimated from the NART, and each of these variables. There was a near significant association between performance on the Eyes test and verbal IQ ($n=48$, $r=0{\cdot}385$, $p=0{\cdot}07$) but not between the total EQ score and verbal IQ.

A multiple regression analysis was performed to include total EQ score, verbal IQ and other demographic factors (sex, age, education and whether the participant was a clinician/academic or not). The only significant predictor of the Eyes test was verbal IQ score (multiple $r=0{\cdot}369$) which accounted for 11·7% of the variance. However, both sex ($r=0{\cdot}266$, $t=1{\cdot}83$, $p=0{\cdot}074$) and EQ score ($r=0{\cdot}255$, $t=1{\cdot}75$, $p=0{\cdot}087$) also approached significance.

Study 2

Participants

An additional 57 volunteers [22 men (38·6%) and 35 (61·4%) women] completed the EQ. These participants were recruited by the first two authors during the course of other projects. These data were combined with those from Study 1 to create a control group of 110 psychologically healthy participants.

In addition, 54 people who contacted the Depersonalization Research Unit at the Institute of Psychiatry, London, reporting symptoms of depersonalization disorder (DPD), were sent the EQ along with some initial mental health screening measures. Some of these people are a subgroup of a cohort reported elsewhere (Baker *et al.* 2003). A further eight people diagnosed with (DPD) at the same unit were also recruited. They completed the EQ during an experimental testing session along with other cognitive measures. As a whole, this group comprised 32 men (51·6%) and 30 women (48·4%), with a mean age of 34·6 (±10·8).

DPD is defined as an 'alteration in the perception or experience of the self so that one feels detached from and as if one is an outside observer of one's mental processes or body' (DSM-IV, 1994). People with DPD also often report a lack of subjective empathy, although the cause and nature of this is unclear. Despite this, there is no reason to expect any difference between the EQ factor structures between the DPD group and healthy individuals, although there may well be a difference in scores.

A χ^2 analysis revealed that the gender distribution was not significantly different between the control and the DPD groups ($\chi^2 = 1{\cdot}26$, df = 1, $p > 0{\cdot}05$). Neither were ages significantly varied between these two groups ($t = -0{\cdot}593$, df = 113, $p > 0{\cdot}05$). For the purposes of analysis, all the groups were combined resulting in 79 (45·9%) men and 93 (54·1%) women [mean age 34·1 years (±10·4)].

Procedure

An exploratory factor analysis, using a principal components analysis (PCA) to construct the initial model, was performed on the EQ. Although the data are ordinal, many authors feel that this procedure is still useful as long as meaningful factors are extracted (Hutcheson & Sofroniou, 1999). The main worry is that it can result in spurious factors where items load according to 'difficulty' (Gorsuch, 1974) and/or that the factors may be harder to interpret (Kim & Mueller, 1978). Both of these issues were kept in mind when interpreting the analysis.

Table 2. *Mean and s.d. EQ scores for entire sample*

		Total score on the EQ			
	n	Mean	s.d.	Min	Max
Male	79	40·9	11·9	15	66
Female	93	49·6	9·6	23	69
Group total	172	45·6	11·6	15	69

Nine cases had missing values ranging from 1 to 4 and were dealt with as described in Study 1. However, one additional participant had a whole page missing and so these values were left as missing.

Results

The mean EQ scores (see Table 2) are remarkably similar to the normative data for both men (mean 41·8 ± 11·2) and women (47·2 ± 10·2) including sex differences ($t = -5{\cdot}34$, df = 147·38, $p = 0{\cdot}001$).

Group comparison

A separate analysis was conducted for each group (DPD *v.* healthy volunteers) to examine the similarity of the factor structure. A PCA followed by an exploratory factor analysis was performed with a varimax rotation. Scree plots were used (Cattell, 1966), as opposed to eigen values which can give rise to many uninterpretable factors. Values less than 0·3 were suppressed.

A salient loading profile (Abdel-Khalek *et al.* 2002) was performed using 0·35 as a cut-off point (see Table 3). These figures were considered along with tentative labels for each of the factors (Tabachnick & Fiddell, 1989) and the decision was made to combine the data.

Data screening

A Pearson's correlation matrix was generated and all EQ items that failed to correlate with any other item at 0·2 (Hutcheson, 1999) or had low communalities in the final model, were removed,

Table 3. *Salient loading analysis*

	No. of salient loadings		Common loadings	
	Control group	DPD group	*n*	%*
Factor 1	12	17	12	100
Factor 2	10	10	8	80
Factor 3	10	9	5	50

* The percentages were calculated in proportion to the control group salient loadings.

namely 15, 18, 28, 37, 38, 39, 49, 60 (see website for Appendix 1).

All EQ items were also re-correlated with the total SDS score. Five EQ items were significantly associated with the total SDS score, namely 11, 18, 34, 37 and 46. Item 37 again showed a negative relationship; however, it also had a low loading as did item 18 (see above), and so this stage of data screening only resulted in the removal a further three items, i.e. 11, 34 and 46. Eleven items were, therefore, left out of the analysis.

Final analysis

There were 29 items and 172 cases, conforming to the five cases per item rule. A PCA with a varimax rotation showed the communalities to lay in the mid range except for items 10 and 57. No. 57 was kept as it loaded onto factor 3 in the final model and no. 10 was removed, as it did not load onto any factors, leaving 28 items in total.

The scree plot showed that only three or four plots (factors) appeared stacked and separate from the rest with the remaining plots falling away and bunched together (see website for Fig. 1). Three factors were kept as it was apparent from both the scree plot and eigen values that they were the strongest, accounting for 41·4% of the total variance.

The item loading for these three factors in the rotated solution are shown in Table 4. Double loadings were allocated on the basis of content, with agreement reached between the first and second authors. The Keiser–Meyer–Olkin measure of sampling adequacy was 0·846 and the Bartlett test of sphericity was highly significant, suggesting the data were suitable for PCA. Factor 1 was labelled 'cognitive empathy', factor 2 'emotional reactivity' and factor 3 'social skills'.

Table 4. *Final loadings from principal components analysis*

	1	2	3
EQ55	0·763		
EQ52	0·726		
EQ25	0·723		
EQ54	0·696		
EQ44	0·688		
EQ58	0·680		
EQ26	0·658		
EQ41	0·633		
EQ19	0·583		
EQ36	0·559	0·315	
EQ1	0·505		0·315
EQ32		0·675	
EQ59		0·658	
EQ42		0·593	
EQ21		0·528	
EQ48		0·508	
EQ6		0·497	
EQ27		0·473	
EQ50		0·466	
EQ43	0·442	0·452	
EQ22	0·322	0·385	
EQ29		0·333	
EQ8			0·771
EQ35			0·768
EQ12			0·619
EQ14			0·575
EQ4			0·538
EQ57			0·398

Validity

The relationship between factors was explored and factors 1 and 2 correlated significantly ($n=171$, $r=0·497$, $p=0·0001$) as did factors 1 and 3 ($n=171$, $r=0·254$, $p=0·001$) and 2 and 3 ($n=171$, $r=0·209$, $p=0·006$). These associations were as expected; however, the co-efficients are not so high as to preclude discriminant validity.

A 3×2 repeated-measures ANOVA was conducted to examine the sex differences by factor. Factor scores were used, as they are a more accurate index of a person's score on a particular factor. Again, there was a main effect of sex [$F(1,169)=19·46$, $p=0·001$] and an interaction between sex and the scores on the different factors [$F(2,338)=5·85$, $p=0·003$]. t tests revealed significant differences on 'cognitive empathy' ($t=-3·083$, df=169, $p=0·002$) and on 'emotional reactivity' ($t=-4·725$, df=169, $p=0·001$) but not on 'social skills' ($t=0·206$, df=169, $p>0·05$).

There was a significant correlation between performance on the Eyes task and the factor scores for 'social skills' ($n=53$, $r=0·273$,

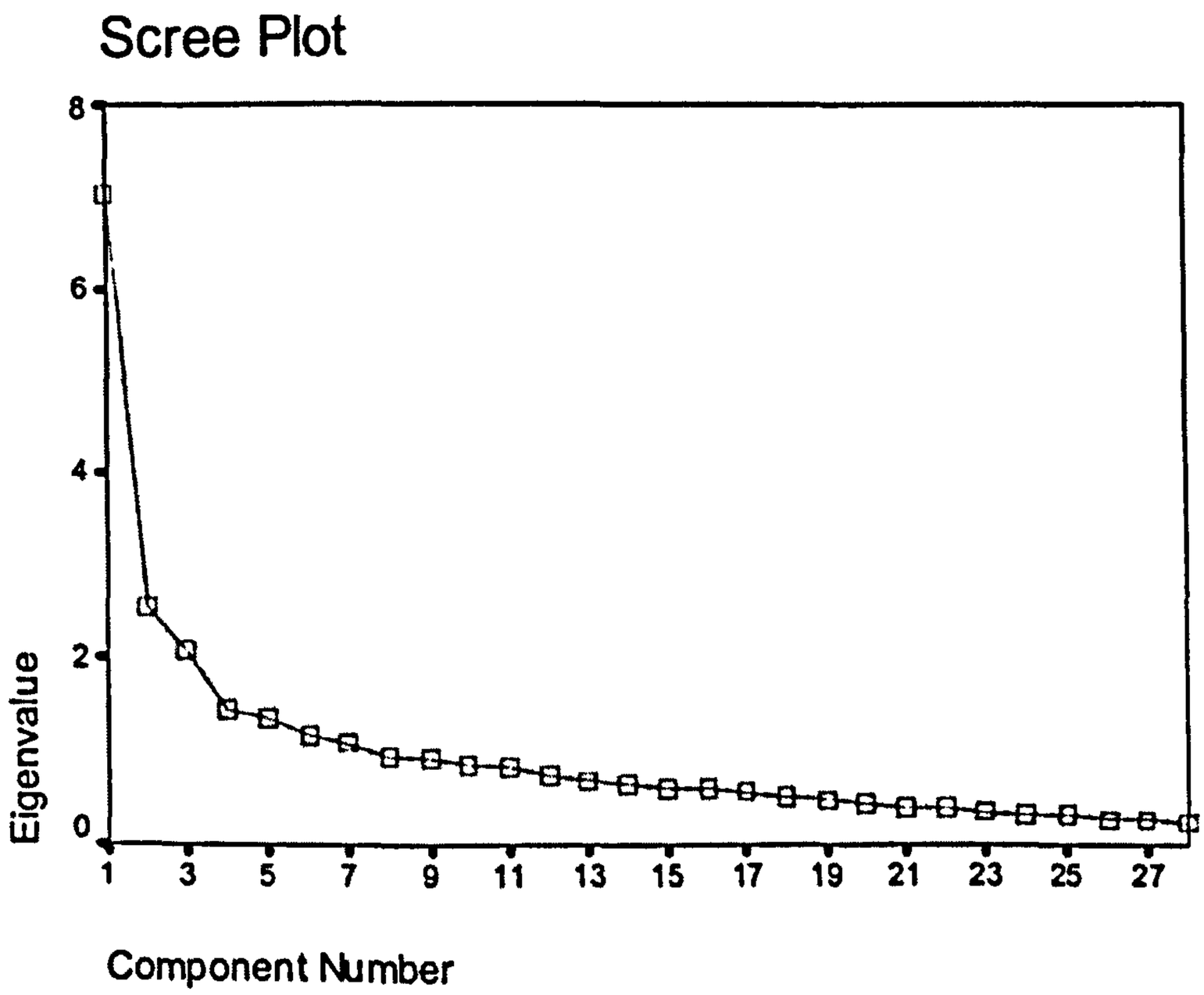

FIG. 1. Scree plot for entire sample.

$p=0{\cdot}048$), but not with either of the other factors. Each factor score was also correlated with predicted verbal IQ as a further check but none had a significant association. The Eyes score, factor scores and demographics (see Study 1) were then entered into a multiple regression analysis. Again, verbal IQ was the only significant predictor with sex approaching significance (see Study 1 for statistics).

Study 3

Participants

Forty-four people were re-contacted 10–12 months after Study 1. A further 4 people who had not taken part in the first studies also participated. The final group consisted of 29 people [11 males (37·9%) and 18 females (62·1%)] with a mean age 32 years (±9·5)]. There were no age differences between this group and the participants in Study 1 ($t=1{\cdot}29$, df=51, $p>0{\cdot}05$) nor was there any difference in sex distribution ($\chi^2=1{\cdot}41$, df=1, $p>0{\cdot}05$). Twenty-four of the original participants returned the EQ and IRI, one person just returned the EQ, and an additional four people filled out the IRI and EQ at time 2 only.

Procedure

Participants were sent both the EQ and the IRI (Davis, 1980). The EQ was re-sent in order to replicate the test–retest reliability observed in the original study. The IRI is a 28-item self-report measure of empathy and so useful for further exploring the EQ's construct validity. It has four subscales, with seven items measured on a 5-point Likert scale ranging from '0 does not describe me well' to '4 describes me very well'. The range of scores for each subscale is 0–35, with 35 representing a high 'empathy' score except on the 'personal distress' scale, which taps self-orientated emotional reactivity.

Results

The test–retest correlation coefficient between EQs administered at time 1 and at time 2 was $r=0{\cdot}835$ ($n=25$, $p=0{\cdot}0001$).

The relationship between the IRI and the total EQ score from test time 2, was explored. Moderate correlations were found between the EQ (without the three items that previously correlated with total SDS score) and both the 'empathic concern' ($n=28$, $r=0{\cdot}423$, $p=0{\cdot}025$) and the 'perspective-taking' subscale ($n=28$, $r=0{\cdot}485$, $p=0{\cdot}009$). The coefficient was $r=-0{\cdot}027$ for the fantasy items ($p>0{\cdot}05$) and $r=-0{\cdot}158$ ($p>0{\cdot}05$) for the 'personal distress'.

The IRI scores were also correlated with the individual factor scores in order to explore concurrent validity. Factor 2, 'emotional reactivity', showed an association with 'empathic concern' ($n=28$, $r=0{\cdot}583$, $p=0{\cdot}001$) and 'perspective taking' ($n=28$, $r=0{\cdot}442$, $p=0{\cdot}019$) but not 'personal distress'. Factor 3 ('social skills'), however, displayed a weak but non-significant relationship with perspective taking ($n=28$, $r=0{\cdot}263$, $p>05$). Factor 1, however, did not correlate significantly with any of the IRI subscales.

Study 4

Participants

The DPD group as described in Study 2.

Measures

The EQ and the Dissociative Experiences Scale version II (DES; Bernstein & Putnam, 1986; Carlson & Putnam, 1993) were administered (see Study 2). The DES is the 'gold standard' measure of DPD. It is a 28-item self-report questionnaire with a cut-off score of 30 for severe dissociative disorders (Carlson & Putnam, 1993). Factor analysis suggests three main components: 'depersonalisation/derealisation (DPD/DR)', 'amnesia' for dissociative experiences and 'absorption' and imaginative involvement (Carlson *et al.* 1991). Eight items make up the DES-Taxon which is sensitive to the detection of DPD with a cut-off score of 13 (Simeon *et al.* 1998).

The Beck Anxiety and Depression Inventories (Beck *et al.* 1988*a*, *b*) were also given to participants due to the co-morbidity between depersonalisation disorder, depression and anxiety (Lambert *et al.* 2001; Baker *et al.* 2003). A score below 11 on either scale is considered within 'normal' range, and a score above 30 is classed as 'severe'.

Table 5. *Mean and s.d. EQ scores for the depersonalisation group*

		Total score on the EQ			
	n	Mean	s.d.	Min	Max
Male	32	38·9	12·4	15	66
Female	30	46·8	10·1	23	65
Group total	62	42·7	11·9	15	66

Analysis

The mean EQ scores (including all the items) can be found in Table 5. No significant differences were found on total EQ score between the psychologically healthy individuals and those with DPD: for men ($t=1{\cdot}208$, df$=77$, $p>0{\cdot}05$) or women ($t=1{\cdot}496$, df$=90$, $p>0{\cdot}054$). The difference between men and women with DPD on total EQ scores again reached significance ($t=-2{\cdot}686$, df$=59$, $p=0{\cdot}009$).

A 3×2 repeated-measures ANOVA showed a main effect for group [$F(1,169)=15{\cdot}11$, $p=0{\cdot}001$] and a significant effect for factor × group [$F(2,338)=12{\cdot}08$, $p<0{\cdot}001$]. *T* tests showed the main difference between groups was on 'social skills' with the DPD group rating themselves as less proficient ($t=6{\cdot}663$, df$=169$, $p=0{\cdot}001$).

Fifty-three people completed the DES, BAI and BDI. The mean score on the BAI was 21·6 (±12) and BDI was 20·3 (±10·5). The mean score on the DES was 23·2 (±14·2), the DPD/DR subscale 36·6 (±24), amnesia 6·2 (±2·5) and absorption 27·6 (±17). The mean score on the DES taxon was 23·3 (±15·4). The BAI, BDI and EQ were all entered into a correlational analysis and the co-efficients were found to be close to zero.

Lastly, the relationship between the BDI, BAI and each factor was examined. 'Emotional reactivity' was significantly related to anxiety scores ($n=52$, $r=0{\cdot}313$, $p=0{\cdot}024$) and 'social skills' showed a significant negative association with depression scores ($n=45$, $r=-0{\cdot}346$, $p=0{\cdot}012$).

GENERAL DISCUSSION

The aim of this study was to examine the reliability, validity and factor structure of the EQ. The mean EQ score was very similar to that found by the original authors indicating the

questionnaires reliability across samples. High test–retest reliability was also shown, as were sex differences mirroring the normative data. However, in Study 1, women scored slightly (but not significantly) higher than the original sample, which may be because a higher proportion of them were drawn from mental health workers. This may prevent firm conclusions regarding sex differences.

The EQ was shown to have concurrent validity as evident from the moderate correlations with the 'empathic concern' and 'perspective-taking' subscales of the IRI (Davis, 1980). The fact that the correlations are only moderate is to be expected, as the total EQ score is an index of global empathy. The weak negative association with 'personal distress' indicates that the two concepts may be inversely related. The lack of association with 'fantasy' items suggests this concept is not empathy *per se* (Baron-Cohen & Wheelwright, in press).

In Study 1, five EQ items correlated significantly with total score on the SDS and three of these were considered of sufficient strength and in the right direction to be left out of the later analysis. In Study 2, one further item was shown to be related to social desirability. The negative correlation with item 37 is somewhat mysterious and may be due to chance factors. That the remaining 35 items showed no association with social desirability supports the scale's construct validity. If the dropped items are to be used in subsequent studies, then it is important to ensure that social desirability is also measured.

The EQ was successfully reduced to a few simple factors which map onto the traditional ideas of empathy, and the final solution accounted for a moderate amount of the total variance. The first factor, cognitive empathy, includes items that measure the appreciation of affective states, i.e. 'I can tell if someone is masking their true emotion', epistemic states, i.e. 'I find it easy to put myself in somebody else's shoes' and desire-based states, i.e. 'I can easily work out what another person might want to talk about'. This is in line with the broader definition of theory of mind as including the attribution of all types of mental state. However, it is also of interest that 'affective state' items had stronger loadings on this factor. This may also explain why no association was found between this factor and the 'perspective-taking' subscale of the IRI, as the latter is geared more towards epistemic states. Whether or not different types of mental state attribution share the same processes is an issue currently under debate (Stone *et al.* 2003).

The second factor, 'emotional reactivity' reflects the tendency to have an emotional reaction in response to others' mental states, i.e. 'seeing people cry doesn't really upset me'. However, the lack of control for 'personal distress' (Davis, 1980), prevents us from labelling this factor 'emotional/affective' empathy. From these data alone, we cannot be sure that the emotional reactions tapped are other- rather than self-orientated. One way round this is to administer the EQ in conjunction with the 'personal distress' items of the IRI (Davis, 1980). This would give an accurate profile of empathic response. Interestingly, although this factor moderately correlated with 'empathic concern' and 'perspective-taking' on the IRI, it was not associated with 'personal distress' items, suggesting it may be tapping empathy after all.

Sex differences (female superiority) were also found on both cognitive empathy and emotional reactivity but not on the last factor, 'social skills'. This contains items that tap the spontaneous use of such skills and/or a lack of intuitive social understanding, i.e. 'I often find it difficult to judge whether something is rude or polite'. Furthermore, an over-reliance on social rules, i.e. 'I consciously work out the rules of social situations', may be indicative of a lack of spontaneous empathy. Social skills seem to rely on a certain amount of cognitive empathy; hence, the relationship with the perspective-taking subscale of the IRI.

The mean score on the Eyes test matched the normative data. The mean EQ score and 'social skills' had weak but significant correlations with this task. Given that it is an implicit, objective measure of cognitive empathy, this relationship may be important. But the fact that neither association reached significance in the regression analysis needs to be considered. Verbal IQ, as estimated by the NART, was the sole predictor in both of the regression analyses. This raises the possibility that the EQ and Eyes task, in fact, tap different constructs. However, the EQ score approached significance as a predictor in Study 1, and the lack of correlation between

verbal IQ and the EQ suggests they are orthogonal. One possibility is that the role of verbal IQ in the Eyes task was confounded by sample selection. Although possible, this explanation is unlikely, as a dichotomous occupation variable designed to control for this bias was not a predictor of performance. It therefore seems that both verbal IQ and total EQ scores may be related to performance on the Eyes task.

In Study 4, people reporting symptoms of DPD did not suffer a global empathy deficit. They showed the same pattern of EQ scores as the psychologically healthy individuals, including sex differences. The near difference between women in the DPD group and controls is very likely to be an artefact of sample selection (see above). The DPD group did, however, report significantly less ability on items tapping 'social skills'. This association is particularly hard to decipher in the presence of co-morbid depression and anxiety. In line with previous reports, this group tended to score within the mild to moderate range on both the BDI and BAI (Lambert *et al.* 2001). The negative association between 'social skills' and the BDI depression scores may provide one explanation for their lack of social competence. However, no firm conclusions can be drawn without objective measures of 'social skills', which do not rely on potentially biased subjective evaluations, i.e. reports from someone who knows the respondent well. Furthermore, the BAI scores also showed a positive relationship with 'emotional reactivity', emphasizing the need to control for anxiety, as well as depression, when measuring 'affective empathy'. It seems that the effects of both on empathy need to be kept in mind, both in clinical settings and the normal population.

This series of studies confirms that the EQ provides a reliable and valid way of measuring empathy via self-report in both healthy individuals and clinical populations. One limitation is the use of ordinal rather than continuous data in the PCA; however, the factors were easily and meaningfully interpretable. A further limitation is the rather disparate and incompletely characterized samples used including the fact that the sample in Study 1 displayed a high verbal IQ as estimated from the NART. However, the consistency observed across studies suggests that the EQ is robust to such demographic factors.

In terms of future work, it is important to tease out the different kinds of emotional reactivity and distinguish between empathic and other types of emotional responses. Furthermore, the effects of transient states such as anxiety and depression should be taken into account. The EQ would appear to have utility in studying at least two clinical groups: people with Asperger's Syndrome and those with neurotic conditions such as DPD which includes anxiety and depressive symptoms. Further use in clinical research would appear to be worthwhile.

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NOTE

Supplementary information accompanies this paper on the Journal's website (http://journals.cambridge.org).

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